P.25.318

BJS

Volume 88
Supplement 1
May 2001

British Journal of SURGERY

53

Association of Surgeons of
Great Britain and Ireland
and
Surgical Research Society

Annual Meeting
Birmingham, 25–27 April 2001

Blackwell
Science

1355-7688(2001)88+1;1-Y

British Journal of Surgery

The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Surgical Research Society, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

Editorial Team

Editors
J. A. Murie, *Edinburgh, UK*
J. R. Farndon, *Bristol, UK*

Associate Editors
P. J. Guillou, *Leeds, UK*
P. R. O'Connell, *Dublin, Ireland*

Website Editor
J. J. Earnshaw, *Gloucester, UK*

Statistical Consultant
G. D. Murray, *Edinburgh, UK*

Council

Chairman
R. C. G. Russell, *London, UK*

Vice-Chairman
T. Bates, *Ashford, Kent, UK*
(Association of Surgeons)

D. Alderson, *Bristol, UK*
J. Bancewicz, *Salford, UK*
M. Büchler, *Berne, Switzerland*
V. W. Fazio, *Cleveland, OH, USA*
K. C. H. Fearon, *Edinburgh, UK*
I. G. Finlay, *Glasgow, UK*
(Royal College of Surgeons)

Treasurer
N. J. McC. Mortensen, *Oxford, UK*

Company Secretary
J. R. C. Sainsbury, *London, UK*

P. Lamont, *Bristol, UK*
(Surgical Research Society)
J. P. Neoptolemos, *Liverpool, UK*
H. Obertop, *Amsterdam, The Netherlands*
M. Rothmund, *Marburg, Germany*
C. J. H. van de Velde, *Leiden, The Netherlands*

Editorial Board

W. H. Allum, *UK*
C. Bassi, *Italy*
J. Beynon, *UK*
N. J. Bundred, *UK*
W. B. Campbell, *UK*
F. Castro-Sousa, *Portugal*
S. C. S. Chung, *Hong Kong*
J. D. Corson, *USA*
D. Demetriades, *USA*
D. M. Dent, *South Africa*
C. Dervenis, *Greece*
T. Diamond, *UK*
L. Fernández-Cruz, *Spain*
A. Fingerhut, *France*
O. J. Garden, *UK*
D. Gotley, *Australia*
D. J. Gouma, *The Netherlands*
P. A. Grace, *Ireland*
U. Haglund, *Sweden*
M. Kitajima, *Japan*
Z. H. Krukowski, *UK*
G. J. Maddern, *Australia*
N. Nagasue, *Japan*
A. R. Naylor, *UK*
S. Nicholson, *UK*
B. Nordlinger, *France*
L. Påhlman, *Sweden*
A. L. G. Peel, *UK*
F. Penninckx, *Belgium*
L. F. Rikkers, *USA*
B. J. Rowlands, *UK*
S. Rudzki, *Poland*
F. Seow-Choen, *Singapore*
O. Soreide, *Norway*
R. A. J. Spence, *UK*
M. D. Stringer, *UK*
K. Sugimachi, *Japan*
J. M. Thomas, *UK*
S. Vittal, *India*
T. N. Walsh, *Ireland*
A. L. Warshaw, *USA*
S. D. Wexner, *USA*
M. H. Wheeler, *UK*

While every effort is made by the Editorial Team, members of Council and the publishers to avoid inaccurate or misleading information appearing in *BJS*, data within the individual articles and advertisements are the responsibility of the authors or advertisers concerned. The BJS Society, the publishers, and members of the Editorial Team and Council accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

Contents

Wednesday 25 April Page no.

08:30–10:30
SRS: Patey Prize 1–8 1

11:00–12:30
SRS: Vascular 1–9 3
SRS: Oncology 1–9 6
SRS: Sepsis/General 1–9 9

13:30–15:30
SRS: Patey Prize 9–16 12

16:00–17:00
SRS: Upper Gastrointestinal 1–6 14

16:00–17:30
SRS: Vascular 10–18 16
SRS: Reperfusion Injury 1–9 19

Wednesday 25 April

09:30–10:00
ASGBI: Superficial Abscesses 1–2 22

16:10–16:40
ASGBI: Emergency Service 1–3 23

17:20
ASGBI: British Obesity Surgery Society 1 24

Thursday 26 April

09:15–10:45
ASGBI: Moynihan 1–6 25
ASGBI: Emergency/General 1–9 27

09:45–10:45
ASGBI: Six of the Best UGI/HPB 30

11:15–12:15
ASGBI: Endocrine/Breast 1–6 32
ASGBI: General 1–6 34
ASGBI: Transplantation 1–6 36

14:00–15:20
ASGBI: Paediatric 1–4 38

14:20–15:10
ASGBI: Trauma/General 1–5 39

14:30–15:30
ASGBI: Six of the Best Breast 40

16:00–17:00
ASGBI: Six of the Best Colorectal 42
ASGBI: Vascular 1–6 44
ASGBI: General 7–12 46

16:30–17:00
ASGBI: Transplantation 7–9 48

The *BJS* ISSN 1355-7688

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *BJS*, Blackwell Science Ltd,
25 John Street, London WC1N 2BS, UK (Tel: +44 0207 404 1831).

Manager Elizabeth Whelan
Production Editor Emma Lawrence
(emma.lawrence@blacksci.co.uk)
Editorial Assistant Emma Pickard

Aims and scope

BJS is the premier general surgical journal in Europe and one of the top surgical periodicals in the world. Its international readership is reflected in the prestigious international Editorial Board, supported by a panel of over 1200 reviewers worldwide.

BJS features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented.

The inclusion of Leading Articles, Reviews and Original Articles means that *BJS* offers an appropriate format for any length or type of submission; in addition, there are abstracts from key meetings, correspondence and book reviews. *BJS* will be of interest not only to general surgeons, but also to specialty surgeons and those working in related fields.

Subscriptions

BJS is published monthly (one volume per annum) in 2001. Subscription prices for 2001 are:

	EUROPE	REST OF WORLD	NORTH AMERICA
Institutional	£146.00	£169.00	$261.00
Individual	£87.00	£101.00	$156.00
All Trainee Surgeons UK and ASIT	£43.50	£50.50	$78.50
Surgeons in Training Worldwide	£43.50	£50.50	$78.50

Subscribers in Canada must add 7% to the subscription price to allow for GST. Subscribers in Europe must quote their VAT registration number or state that they are not registered. Subscribers in the following countries who are not VAT-registered must add VAT at the appropriate rate:

Belgium (6% TVA/BTW)
France (2.1% TVA)
Germany (7% MWST)
Spain (4% IVA)
The Netherlands (6% BTW)

Orders for current subscriptions and back issues should be sent to Blackwell Science Ltd, Journal Subscriptions, PO Box 88, Oxford OX2 0NE, UK. Tel: +44 1865 206180; Fax: +44 1865 206219; e-mail: jnl.orders@blacksci.co.uk

Despatch

BJS is despatched within the UK by second class post, within Europe by air mail, and to other continents by various forms of air-speeded delivery, to the USA by air freight for forwarding by second class post*, to India by air freight for guaranteed local delivery, and to all other countries by accelerated surface post. Add to the cost of a regular subscription £24.00/$36.00 for air mail delivery outside Europe.

Business correspondence

All other business correspondence, including orders for offprints (offprints@blacksci.co.uk) and advertising space (advert@blacksci.co.uk) should be addressed to:
BJS, Blackwell Science Ltd, Osney Mead,
Oxford OX2 0EL, UK. (Tel. +44 1865 206206;
Fax: +44 1865 721205).

Copyright and photocopying

© 2001 Blackwell Science, acting as agents for the BJS Society. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Science for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $15 per copy is paid directly to CCC, 222 Rosewood Drive, Suite 910, Danvers, MA 01973, USA. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to the publisher.

Paper

The Publisher's policy is to use acid-free permanent paper, to the draft standard ISO/DIS/9706, made from sustainable forests using chlorine-free pulp. The paper used in this journal has an ECO-CHECK 4-star rating.

BJS has a worldwide website at: http:// www.bjs.co.uk

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the publisher.

© 2001 Blackwell Science Ltd

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

Contents (*continued*)

Friday 27 April

09:15–10:15

ASGBI: Six of the Best Vascular 49

09.15–10.45

ASGBI: Colorectal 7–15 51
ASGBI: Upper Gastrointestinal 1–9 53

11:15–12:15

ASGBI: Colorectal 16–21 56

14.00–16:00

ASGBI: Hepatobiliary 1–12 58

14:15–16:05

ASGBI: Vascular 13–24 62

Posters 1–71 65

Author Index 83

Association of Surgeons of Great Britain and Ireland

2001 MOYNIHAN TRAVELLING FELLOWSHIP AND DINWOODIE AWARDS

The Association of Surgeons of Great Britain and Ireland represents all general surgeons throughout the United Kingdom and the Republic of Ireland. An annual Travelling Fellowship up to the value of £4,000 is available by open competition to Specialist Registrars towards the end of higher surgical training or Consultants within three years of appointment at the closing date of this advert, to enable them to broaden their education and to present and discuss their contribution to British and Irish surgery overseas. The Dinwoody Trust will offer one or two further awards of approximately £1,500.

Candidates must be residents of the United Kingdom or the Republic of Ireland but need not be either Fellows or Affiliate Fellows of the Association; however they should be engaged in general surgery or in one of its specialties. A full Curriculum Vitae should be submitted giving details of past and present appointments and publications, together with a detailed account of the proposed programme of travel, costs involved and objectives to be achieved. Shortlisted candidates will be interviewed by the panel at the Association, at 4.30pm on Tuesday 20 November 2001. The panel will pay particular attention to originality, scope and feasibility of the proposed itinerary. The successful candidate will be expected to act as an ambassador for British and Irish Surgery and should be fully acquainted with the aims and objectives of the Association of Surgeons and its role in surgery. After the visit the successful candidate will be asked to address the Association at its Annual General Meeting.

Deadline for applications: **Monday 15 October 2001**

Applications (15 copies) and requests for information should be submitted to the Honorary Secretary, Association of Surgeons of Great Britain and Ireland, at the Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PE.

2001 OVERSEAS SURGICAL FELLOWSHIP

The Association of Surgeons of Great Britain and Ireland, together with the **British Journal of Surgery Society**, are offering £10,000 per annum to sponsor surgeons wishing to work on a short term basis, primarily in the Third World. This Scheme is run in conjunction with the Tropical Health and Education Trust to provide support for overseas medical schools in the development of their undergraduate and postgraduate training programmes and also for research, thereby, establishing links with these centres.

Only Fellows including Full, Senior, Associate and Affiliates of the Association of Surgeons may apply and if successful, a grant of up to £2,000 will be made available to individual applicants.

Deadline for applications: **Monday 15 October 2001**

Further details are available from Miss J Rabone, The Association of Surgeons of Great Britain & Ireland, at the Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PE Tel: 020 7973 0300 Fax: 020 7430 9235.

Association of Surgeons of Great Britain and Ireland Council 2000/2001

President
Mr D F L Watkin

Honorary Treasurer
Mr T Bates (SE Thames)

To retire in 2002
Mr J Doran (Trent)
Mr D McCarthy (Wales)
Mr A Shandall (Wales)
Mr P Edwards (Mersey)
Mr R Maxwell (N Ireland)
Mr S Meehan (North Western)

To retire in 2003
Mr J Collin (Oxford)
Mr J Ferguson (Scotland)
Mr H N Ross (NE Thames)
Mr J Wolfe (NW Thames)
Mr J L Duncan (Scotland)
Mr M Lee (West Midlands)
Mr S Raimes (Northern)

Honorary Secretary
Mr G T Layer (SW Thames)

Honorary Editorial Secretary
Professor J R Farndon (South Western)

To retire in 2004
Mr R W Talbot (Wessex)

To retire in 2005
Mr J Macfie (Yorkshire)
Professor W A Tanner (Ireland)

Ex-officio

Vice President	Mr R C G Russell
Vice President-Elect	Mr R W G Johnson
Chairman – Scientific Committee	Professor B J Rowlands
Chairman – Education Committee	Mr R E C Collins
Chairman – Private Practice Committee	Mr R C G Russell

President/Representatives of the Sub-Specialty Associations

Association of Coloproctology of Great Britain and Ireland
Mr P Lee
Association of Endoscopic Surgeons of Great Britain and Ireland
Mr R W Motson
Association of Upper Gastrointestinal Surgeons
Professor D Alderson
British Association of Endocrine Surgeons
Professor J R Farndon
British Association of Surgical Oncology/Breast Group
Professor R E Mansel
British Transplantation Society
Professor A Bradley
Vascular Surgical Society of Great Britain and Ireland
Mr R N Baird

Honorary Archivist
Mr M K H Crumplin

Observers

UEMS Monospecialist Committee in General Surgery
Professor R M Greenhalgh

SAC
Mr A E B Giddings – Chairman, Mr R A Cobb, Professor S M Griffin, Mr K Horgan, Mr P M Lamont, Dr Ruth McKee, Professor R J Nicholls and Professor M Wheeler.

ASIT
Mr J F Hossain

Armed Forces
Colonel P Roberts

Surgical Research Society

The constitution of the SRS Committee is as follows:

President
Professor D Bouchier-Hayes

Honorary Secretary
Professor J R T Monson

Honorary Treasurer
Professor J N Baxter

Editorial Secretary
Mr P M Lamont

Educational Co-ordinator
Mr N J Bundred

Web Master
Professor A Darzi

Membership Development
Professor H P Redmond

Research Co-ordinator
Mr P McCulloch

Member
Professor M L Nicholson

Member
Mr C D Johnson

Surgeon in Training
Mr P J Drew

Non-clinical Scientist
Dr S A Waton

Association of Surgeons of Great Britain and Ireland and Surgical Research Society

---

The combined meeting of these societies occurs in Birmingham this year. The *British Journal of Surgery* continues to enjoy its association with these two affiliated societies in the production of this abstract supplement.

The *BJS* is pleased to see a further collaborative meeting and remains responsive to the needs of its affiliate societies. It will continue to produce journals and supplements that reflect the activities of these groups, and enjoys receiving manuscripts based on presented papers.

The Editors of the *BJS* wish all participants an enjoyable and fruitful meeting in Birmingham.

The Editors
BJS

SRS: Patey Prize 1–8

Wednesday 25 April 2001 08:30–10:30

Patey Prize 001

Role of urokinase-type plasminogen activator in venous thrombus resolution

I Singh, A. Smith, M Collins, M Waltham and K.G Burnand
Department of Surgery, St Thomas' Hospital, London, UK

Aims: To determine whether urokinase-type plasminogen activator (uPA), a facilitator of cell migration, has a role in venous thrombus resolution
Methods: Thrombi were induced in the infra-renal *vena cavae* of adult uPA knockout (uPA-/-) and wild-type (control) mice (total $n = 68$) by intermittent compression with a vascular clip and the application of a ligature to produce a partial stenosis Thrombi were harvested at 1, 7, 10, 14, 21 and 28 days, fixed and embedded in paraffin Serial transverse sections were obtained at intervals along the entire length of each thrombus and stained with haematoxylin and eosin and Martius Scarlet Blue. The size of the thrombi (calculated as the area of thrombus occupying the vein lumen) and the amount of recanalization (calculated as the area between the thrombus and the vein wall) was measured using computerassisted image analysis
Results: There was no significant difference in thrombus area at day 1 between the two groups of mice ($P = 0.63$, Mann–Whitney) By 4 weeks the area of thrombus in the control mice had reduced to one-sixth of their original size ($P < 0.01$, Mann–Whitney), whilst the thrombus in the urokinase knockout mice remained the same ($P = 0.14$, Mann–Whitney) The thrombus size during the 28 days in the wild type mice was significantly smaller than in the urokinase knockout mice ($P = 0.0001$, ANOVA) At 28 days the wild-type mice had a 10-fold higher recanalization area compared with the uPA knockout mice ($P < 0.01$, Mann–Whitney)

	Mean thrombi size (mm^3) [SE]		Recanalization (per cent)	
	Wild-type	uPA-/-	Wild-type	uPA-/-
1	1.88 [0.25]	1.64 [0.31]	3 [0.3]	3 [1.9]
7	1.56 [0.12]	2.52 [0.23]	4 [0.6]	2 [0.2]
10	1.00 [0.25]	1.29 [0.22]	9 [3.8]	8 [2.2]
14	0.50 [0.06]	1.86 [0.34]	18 [3.1]	7 [2.6]
21	0.25 [0.06]	1.37 [0.28]	35 [4.3]	7 [1.2]
28	0.31 [0.05]	2.26 [0.20]	29 [4.6]	3 [0.6]

Conclusions: Venous thrombi fail to resolve in urokinase-deficient mice This suggests that urokinase plays an important role in venous thrombus resolution

Patey Prize 002

Supplemental bovine colostrum attenuates small intestinal ischaemia–reperfusion injury in rats

K H McCune, P Erwin, M. McCaigue and K.R. Gardiner
Department of Surgery, Queen's University, Belfast, UK

Aims: Colostrum contains growth factors, nutrients and anti-oxidants, which are known to enhance intestinal mucosal healing It was therefore hypothesized that pretreatment with bovine colostrum would protect the small intestinal mucosa against injury in a rat model of mesenteric ischaemia–reperfusion
Methods: Sixty male Wistar rats (250–300 g) were divided into three equal groups. Groups 1 and 2 were gavaged for days with 2 mL water day^{-1}; group 3 was gavaged with 2 mL (100 mg mL^{-1}) bovine colostrum (Symbiotics, Arizona) per day There was free access to water and chow. Under anaesthesia (ketamine 100 mg kg^{-1} and xylazine 20 mg kg^{-1} intraperitoneal injection), group 1 underwent laparotomy for 90 min (sham operation); in groups 2 and 3 the superior mesenteric vessels were occluded for 30 min followed by a 60-min reperfusion period At the end of 90 min, intracardiac blood was taken for plasma interleukin-6 (IL-6) assay (ELISA) and a 1 cm terminal ileal segment excised for histological measurement of mucosal thickness An everted ileal sac, length 8 cm, was created and the mucosal-to-serosal permeability (Perm) to ^{14}C-labelled polyethylene glycol measured *in vitro* in a shaking water bath at 37°C
Statistics: Mann–Whitney and *t*-tests; significance taken as $P < 0.05$
Results: Data are expressed as mean ± SEM.

Group	IL-6 (pg mL^{-1})	Mucosal thickness (μm)	Perm (counts min^{-1})
1	37.8 ± 11.3	0.45 ± 0.01	82.7 ± 17.3
2	184.4 ± 19.1*	0.29 ± 0.008 *	144.7 ± 8.3*
3	52.1 ± 15.9#Ψ	0.33 ± 0.0*#Ψ	109.6 ± 9.4#Ψ

*$P < 0.01$ *versus* group 1, #$P < 0.01$ *versus* group 2, Ψns *versus* group 1

Conclusions: Pre-treatment with supplemental bovine colostrum reduced mucosal injury (as measured by mucosal thickness and permeability) and IL-6 release in a rat model of mesenteric ischaemia and reperfusion

Patey Prize 003

Nitric oxide in ischaemic preconditioning of the liver

R.S Koti, M.R Dashwood, A.M. Seifalian and B R. Davidson
University Department of Surgery and Liver Transplantation Unit, Royal Free and University College Medical School, Royal Free Hospital, London, UK

Aims: Ischaemic preconditioning (IPC) may protect the liver against subsequent ischaemia via nitric oxide (NO) formation.
Methods: Sprague–Dawley rats were subjected to 45 min lobar ischaemia followed by 2 h reperfusion (IR). L-arginine or L-NAME were administered to stimulate or block NO synthesis Study groups (n = 6) had. (1) sham laparotomy; (2) IR, (3) IPC with 5 min ischaemia and 10 min reperfusion before IR; and (4) L-arginine before IR (5) L-NAME + IPC before IR Liver function tests, tissue ATP levels and serum nitrates were analysed. Identification of nitric oxide synthase (NOS) was carried out using NADPH-diaphorase on slide-mounted tissue sections. Data was analysed using analysis of variance (ANOVA) for multiple comparisons and paired Student's test
Results: Both IPC and L-arginine treatment increased serum nitrates (μM, 93.8 ± 4.3 and 84.0 ± 4.7 *versus* 18.4 ± 2.3 (IR), both $P < 0.05$) and, improved tissue ATP μmol g^{-1}, 10.0 ± 0.8 and 8.0 ± 0.6 *versus* 5.0 ± 0.1 (IR), both $p < 0.05$) and serum liver enzymes(U L^{-1}, ALT = 1380 ± 320 and 1257 ± 970 *versus* 5173 ± 215 (IR), AST = 1537 ± 113 and 1501 ± 731 *versus* 3103 ± 190 (IR), all $P < 0.05$) These effects were prevented by L-NAME administration (nitrates = 17.3 ± 1.7 μM, ATP = 4.3 ± 0.2 μmol g^{-1}, ALT = 5962 ± 317 U L^{-1}, AST = 3653 ± 211 U L^{-1}, all $P < 0.05$ *versus* IPC and L-arginine) NOS detected by NADPH diaphorase was expressed by sinusoidal endothelium and was induced by IPC and L-arginine
Conclusions: IPC resulted in a hepatoprotective effect and, was associated with increased nitrates and greater NOS content in the liver. These data are suggestive of a role for nitric oxide in IPC

Patey Prize 004

Antisense gastrin gene transfection affects cell proliferation and COX-2 expression

A.D Gilliam, D. McWilliams and S A. Watson
Cancer Studies Unit, University Hospital, Nottingham, UK

Background: Gastrointestinal (GI) tumours are known to express both cyclo-oxygenase-2 (COX-2) and gastrin, both of which play a role in cell proliferation/apoptosis. Gastrin up-regulates *Reg* gene and amphiregulin expression therefore the aim of this study was to determine whether gastrin also increased gene expression of COX-2
Methods: A series of GI cell lines were stably transfected either with a control or gastrin antisense vector (PCR3.1) Three gastric cell lines (MGLVA1 and AGS), two pancreatic (MiaPaCa2 and Pan1), and one oesophageal (OE21), were successfully transfected, as confirmed by Southern blotting with a relevant oligoprobe Cell proliferation was assessed using the colorimetric MTT assay and COX-2 mRNA expression was quantified by real time PCR using the SYBR green fluorescent dye
Results: All cell lines transfected with gastrin antisense had significantly reduced basal growth in serum-free medium (43–50% inhibition, $P = 0.01$, Student's *t*-test) COX-2 gene expression was reduced in all cell lines (mean of 56% inhibition, $P = 0.087$ paired Student's *t*-test)
Conclusions: Gastrin may play a role in the over-expression of COX-2 in upper GI tumours

Patey Prize 005

The null polymorphism of the glutathione-S-transferase gene (GST-T1) is protective in acute pancreatitis

S H Rahman, K Ibrahim, M. Larvin and M J. McMahon
Academic Unit of Surgery, The General Infirmary, Great George Street, Leeds LS1 3EX, UK

Aim: To determine the prevalence of genetic polymorphisms of the glutathione-S-transferases μ (GST-M1) and Ψ (GST-T1) in patients with

acute pancreatitis (AP). In addition, to establish whether these polymorphisms would confer an increased susceptibility to severe disease.
Method: Patients with a diagnosis of AP based on raise amylase (3 × normal) or CT evidence were recruited within 24-hrs of presentation of abdominal pain. DNA extracted from peripheral leukocytes was genotyped by PCR. The peak C-reactive protein level (CRP) at 96 h was used as a marker of the severity of the systemic inflammatory response (SIR).
Results: In total, 137 patients with AP (37 severe) and 206 healthy controls were studied. The prevalence of the GST-T1*O (null) genotype was significantly reduced in all patients with AP (24%) compared to controls (30.6%, $P=0.01$) and in particular when AP was secondary to gallstones (14.1%, $P<0.01$). In severe attacks the GST-T1*O was significantly under-expressed (2.7%) compared to patients with mild attacks (23%, $P=0.002$) and healthy controls ($P=0.0001$). In all AP patients, the GST-T1*A genotype was associated with higher CRP levels (median 172 g dL^{-1}, range 4–476) than patients with the null genotype (median 90 g dL^{-1}, range 5–257, $P<0.05$). Dichotomized variable analysis suggested the GST-T1*A genotype conferred increased susceptibility to a severe attack independent of the GST-M1 genotype.
Conclusion: The GST-T1*O (null) polymorphism appears to be protective in acute pancreatitis. Individuals possessing the GST-T1 gene appear to mount a greater acute phase protein response in AP.

Patey Prize 006

Recipient-derived hepatocytes identified in human transplanted livers express albumin: detection using simultaneous indirect immunofluorescence staining and Y chromosome painting

S.R. Dundas,[1] S. Boyle,[3] J.A. Ross,[1] C.O. Bellamy,[2] W. Hawkins,[1]
W. Bickmore,[3] and O.J. Garden[1]

Departments of [1]Clinical and Surgical Sciences and [2]Pathology, University of Edinburgh, EH3 9YW and [3]MRC Human Genetics Unit, Edinburgh EH4 2XU, UK

Aims: To determine the origin of chimeric hepatocytes and cholangiocytes in transplanted livers and investigate the functional status of chimeric hepatocytes.
Methods: Archival tru-cut biopsies of five female-to-male adult human liver transplants were analysed. Formalin-fixed paraffin-embedded tissue sections were 'painted' for the Y-chromosome using fluorescence *in situ* hybridization (FISH) or stained with antibody-recognising albumin detected by indirect immunofluorescence combined with FISH. Stained cells were visualized using triple colour fluorescence confocal microscopy.
Results: Pre-perfusion biopsies of the female donor livers did not contain Y-chromosome-positive cells, indicating that the five livers were not chimeric for the Y chromosome through transplacental passage of male fetal cells. Protocol biopsies taken seven days after transplant revealed Y-chromosome-positive blood cells. In repeat biopsies taken at 1–7 years after transplant, cells with hepatocyte morphology and epithelial cells incorporated into ducts were observed and a proportion of these displayed Y-chromosome positivity. Up to 20% of hepatocytes were of recipient origin in certain grafts and simultaneous immunofluorescence and FISH analysis revealed that Y-chromosome-positive hepatocytes also stained positively for albumin.
Conclusions: Simultaneous indirect immunofluorescence staining and chromosome painting is feasible on paraffin-embedded tissue sections, and demonstrates for the first time that liver transplant recipients generate cholangiocytes and functional hepatocytes from cells infiltrating the graft. Modulating the hepatic differentiation of circulating cells may provide the basis for novel future clinical therapies.

Patey Prize 007

Glutamine prevents TNFα-induced bacterial translocation

E.C. Clark,[1,2] G. Warhurst[2] and G.L. Carlson[1,3]

Departments of [1]Surgery, [2]GI Science & [3]MRC Trauma Unit, Hope Hospital, Salford, UK

Aims: Glutamine may reduce septic morbidity in critical illness but the mechanisms are unclear. The aim of this study was to test the hypothesis that glutamine availability influences bacterial translocation across intestinal epithelia and to provide an understanding of the underlying cellular mechanisms.
Methods: Human-derived intestinal epithelial cells (CACO2) were grown as confluent polarized monolayers in a bicameral system (Transwell) in DMEM containing 2mM glutamine. Cells were then incubated with TNFα (20ng mL^{-1}) for 6 h, with ($n=6$) or without ($n=6$) prior removal of glutamine. Reversibility and specificity of glutamine effects were assessed by replacing glutamine in the culture for 2 h ($n=6$) or adding an isonitrogenous mixture of non-essential amino acids ($n=6$). Finally cells in glutamine containing medium were incubated with and without TNFα (20ng mL^{-1}) for 6 hr in the presence of 0.6 mM aminooxyacetate, an inhibitor of glutamine oxidation ($n=8$), or 3.2 mM buthionine sulfoximine, an inhibitor of glutamine conversion to glutathione ($n=8$). In each study the ability of a 10^3 CFU inoculum of *E. coli* C25 to translocate across the epithelium from apical to basal chambers after 4 h incubation was measured by Miles and Misra serial dilution assay. All results are expressed as mean ± SD and comparison between groups made with Student's *t*-test.
Results: Glutamine deprivation or incubation with TNFα alone had no significant effect on bacterial translocation *versus* control (3.6 ± 0.4 and 3.7 ± 0.5 *versus* 3.4 ± 0.3 log CFU mL^{-1}, respectively, $P=$ns). However, glutamine deprivation significantly increased bacterial translocation in the presence of TNFα *versus* control (5.5 ± 0.4 *versus* 3.3 ± 0.3 log CFU mL^{-1}, $P<0.001$). Replacing glutamine for 2 hr completely reversed the change in translocation (3.5 ± 0.4 *versus* 3.4 ± 0.2 log CFU mL^{-1}, $P=$ns) but the isonitrogenous amino acid mixture did not (5.0 ± 0.4 *versus* 3.3 ± 0.4 log CFU mL^{-1}, $P<0.001$). Treatment with aminooxyacetate facilitated translocation in the presence of TNFα, *versus* controls (5.3 ± 0.3 *versus* 3.3 ± 0.2 log CFU mL^{-1}, $P<0.001$) but buthionine sulfoximine did not (3.4 ± 0.3 *versus* 3.3 ± 0.2 log CFU mL^{-1}, $P=$ns).
Conclusions: Acute glutamine depletion sensitizes the intestinal epithelial cells to TNFα-induced bacterial translocation. These changes are specifically reversible with glutamine and rely upon the use of glutamine as a metabolic fuel by the enterocyte and not glutathione synthesis.

Patey Prize 008

Endovascular repair of abdominal aneurysm minimizes intestinal mucosal and glomerular dysfunction

S. Junnarkar, L.L. Lau, D. Underwood, M.G. Smye, B. Lee,
R.J. Hannon and C.V. Soong

Vascular Unit, Belfast City Hospital, Belfast BT9 6AB, UK

Aims: An increase in intestinal permeability and renal dysfunction has been demonstrated in patients after elective and emergency abdominal aortic aneurysm (AAA) repair. This study aims to evaluate if endovascular repair (EVR) of abdominal aortic aneurysm can lead to a preservation of intestinal mucosal barrier and renal functions compared to open repair (OR).
Methods: Eight patients admitted for elective infrarenal AAA repair underwent OR while seven had EVR. Intestinal permeability was assessed preoperatively (D0), at day 1 (D1) and day 3 (D3) after surgery using the lactulose/mannitol (L/M) differential excretion test while renal glomerular permeability was assessed by measuring the microalbumin-creatinine clearance ratio (ACR). Serum concentrations of creatinine and urea were measured preoperatively (D0), and daily for 5 days postoperatively.
Results: A significant increase in intestinal permeability was found in the OR group at D1 (0.08 ± 0.04) (mean ± SEM) and D3 (0.04 ± 0.007) when compared with D0 (0.015 ± 0.002, $P<0.05$). This was also significantly greater in the OR group compared to the EVR group at D3 (0.011 ± 0.004, $P<0.05$). The change in ACR was expressed as a percentage of baseline due to the difference in this level observed between the two groups. A significant difference was observed in the percentage rise in ACR on D1 in the OR group (812% ± 241) compared to the EVR group (86% ± 26, $P<0.05$). No change was seen in serum creatinine or urea concentrations in both groups.
Conclusion: The results suggest that the increase in intestinal and glomerular permeability observed during open aortic surgery may be reduced if the endovascular technique is used.

SRS: Vascular 1–9

Wednesday 25 April 2001 11:00–12:30

Vascular 001

Evaluating quality-of-life changes in intermittent claudication

P.F S. Chong, A M. Garratt,[1] J Golledge, R M Greenhalgh and A.H Davies

Department of Vascular Surgery, Imperial College School of Medicine, Charing Cross Hospital, London and [1]Unit of Healthcare Epidemiology, Institute of Health Sciences, Oxford University, Oxford, UK

Introduction: As yet, no intermittent claudication (IC)-specific instrument is available for the assessment of quality of life (QOL) following treatment. Following development and validation, a symptom-specific questionnaire (SSQ) was tested for responsiveness in a series of patients with IC undergoing conservative therapy or angioplasty

Methods: Resting ankle pressures (ABPI) and SSQ were assessed before conservative treatment (risk factor modulation + exercise and smoking cessation advice) or angioplasty At 3 months all patients completed a symptom transition question (STQ) (worse = 0, same = 1, better = 2) before ABPI and SSQ scores were repeated. SSQ responsiveness to symptomatic change was also compared to the WIQ (Walking Impairment Questionnaire), EuroQol and the SF-36 using the standardized response means (SRM) – the ratio of the mean change in score/standard deviation of the change

Results: A total of 100 patients underwent assessment (*$P<0$ 01).

Table 1 Symptomatic results and ABPIs

	Conservative	Angioplasty
Total no of patients	60	40
Symptoms better (STQ=2)	27%	78%
Symptoms same or worse (STQ=0 or 1)	73%	22%
Median ABPI		
0 months	0 66 (0 36–0 90)	0 69 (0 38–0 97)
3 months	0 66 (0 38–1 0)	0 93 (0 35–1 0)

Table 2 SSQ mean scores (±SD)

	0 months	3 months
*Conservative		
(STQ=0) $n=10$	55 28 (20 02)	64 50 (16 62)
(STQ=1) $n=34$	39 22 (18 85)	37 80 (18 97)
(STQ=2) $n=16$	42 42 (19 54)	37 91 (22 69)
Angioplasty		
(STQ=0 or 1) $n=9$	56 25 (9 08)	46 63 (21 59)
*(STQ=2) $n=31$	55.38 (18 60)	29 10 (20 65)

SRM for STQ=2 were −1.37 (SSQ), 0 83 (WIQ walking distance), 0.50 (EuroQol) and 0 57 (SF-36 General Health Perception) SRM for STQ=0 were 1.06 (SSQ), −0 46 (WIQ walking distance), −0 34 (EuroQol) and −0 64 (SF-36).

Conclusions: The SSQ was the most responsive QOL measure in the study At 3 months, patients who improved post-angioplasty had the best and patients who deteriorated with conservative therapy had the worst mean SSQ scores. Angioplasty demonstrated good symptomatic improvement at 3 months.

Vascular 002

The association between plaque vascularity and symptomatic carotid occlusive disease

R. Mofidi, P McCarthy, D. Mehigan, S J Sheehan, T Crotty and T V Keaveny

Department of Vascular Surgery and Pathology St Vincent's University Hospital, Dublin, Ireland

Introduction: Angiogenesis is a well-described feature of atherosclerotic lesions. It has been described in association with symptomatic carotid occlusive disease and unstable coronary syndromes. The aim of this study was to confirm the association between plaque vascularity and development of ipsilateral neurological symptoms

Methods: From February 1999 to April 2000, consecutive patients undergoing carotid endarterectomy for carotid stenosis were considered

Patients who had been symptomatic in the last 30 days prior to surgery were included while plaques obtained from asymptomatic patients undergoing carotid endarterectomy were used as controls. Endarterectomy specimens from these patients were examined and divided to their constituent atherosclerotic lesions. Histological sections were prepared and stained with haemtoxylin and eosin and immunohistochemically with an endothelial cell marker (CD-34). Microvessel counts are performed in CD-34 stained sections at ×400 magnification and were verified through computerized image analysis. Mann–Whitney U-test was used to study the differences in microvessel counts in symptomatic and asymptomatic patients

Results: Seventy-three patients underwent carotid endarterectomy of which 28 (17 symptomatic, 11 asymptomatic) fulfilled the criteria for inclusion to the study Higher microvessel counts were observed in atherosclerotic plaques obtained from symptomatic patients [median 203 (range 59–398)] compared with patient who did not have any symptoms prior to surgery [median 78 (range 14–156)] ($P<0$ 0001)

Conclusions: This study confirms the relationship between presence of intimal angiogenesis and recent ipsilateral hemispheric neurological events Knowledge of the role of these new blood vessels in carotid atherosclerotic lesions will further advance our understanding of the process that is responsible for development of carotid plaque instability leading to stroke

Vascular 003

Chlamydia pneumoniae antigens cause experimental aortic dilatation: an effect counteracted by azithromycin

J R S. Tambiah and J T. Powell

Department of Vascular Surgery Imperial College at Charing Cross Hospital, London W6 8RP, UK

Aims: There is contemporary debate over the possible causative role of *Chlamydia pneumoniae* in cardiovascular disease, including abdominal aortic aneurysms, with Koch's postulates remaining unsatisfied We have investigated the role of *Chlamydia pneumoniae* in causing experimental aortic dilatation and inflammation and whether a macrolide antibiotic or non-steroidal anti-inflammatory drug could attenuate these effects.

Methods: *Chlamydia pneumoniae* preparations (10^8 organisms mL^{-1} in 0.2 M $CaCl_2$), or $CaCl_2$ alone, were applied, at laparotomy, to the abdominal aortic adventitia of cholesterol-fed rabbits (mean serum cholesterol 78 mmol L^{-1}) The preparations included either live organisms, formalin-inactivated organisms (retaining membrane and heat shock protein antigenicity) or heat-inactivated organisms (destroying membrane antigens but retaining lipopolysaccharide activity). Aortic diameters were measured by ultrasonography After 3 weeks the aorta was removed at post-mortem and analysed for the presence of bacterial DNA (nested polymerase chain reaction for the *omp-1* gene) and number of macrophages (RAM-11 immunostaining and image analysis) Oral azithromycin or carprofen were given to some rabbits

Results: There was no significant weight gain in cholesterol-fed rabbits between laparotomy and post-mortem The mean serum cholesterol concentration was Organism doses of $\leq 0\ 5 \times 10^8$ had no effect

Chlamydia pneumoniae	*n*	Drug	Diameter increase (per cent)	Chlamydial DNA in aorta	Macrophage count per unit area
None	6	None	19±7	0/2	5 6±6
Heat-inactivated	4	None	54±16	0/4	26 6±15
Live	4	None	125±25*	2/4	342±144*
Formalin-inactivated	5	None	98±198*	2/5	143± 69*
Formalin-inactivated	4	Azithromycin	7±13†	Nd	3 3±4 5†
Formalin-inactivated	4	Carprofen	0†	Nd	109±5*

Results are given as mean ± SD Nd, not determined ,*†ANOVA significant difference from rows 1 & 4, respectively, $P<0$ 02

Conclusions: *Chlamydia pneumoniae* facilitates aortic dilatation by an antigen-mediated inflammatory response (possibly via molecular mimicry), rather than an infectious mechanism Azithromycin abrogates these effects, probably by quenching the inflammatory stimulus of chlamydial antigens, and might have similar beneficial effects in human abdominal aortic aneurysms

Vascular 004

Capillary morphology of patients with chronic venous disease of lower limb

M.H. Howlader and P.D. Coleridge Smith

Royal Free and University College Medical School, London, UK

Aims: Patients with lipodermatosclerosis (LDS) due to chronic venous disease (CVD) show proliferation and convolution of their skin capillaries. Our aim was to quantity capillary damage in patients with CVD using capillary microscopy.

Methods: Sixty patients with CVD were examined and assigned to the appropriate CEAP clinical stage. All patients underwent duplex ultrasonography to confirm the extent of venous disease. Ten control subjects with no arterial or venous disease of the lower limb were also studied. Images of the skin microcirculation were obtained using a CAM1 microscope (KK Technology, UK). In patients with skin changes the most severe regions of lipodermatosclerosis were studied. In all other subjects the region 5 cm proximal to the medial malleolus was investigated. The total number of visible capillaries was counted in a 2.4 mm^2 region. Within each capillary, the number of convolutions was counted.

Results: Patient supine. All data: median (interquartile range).

CEAP stage	CO ($n = 10$)	C1 ($n = 10$)	C2 ($n = 10$)	C3 ($n = 10$)	C4a ($n = 10$)	C4b ($n = 10$)	C5 ($n = 10$)
Clinical type	Control	Dermal flares	VVs	Oedema	Skin changes	LDS	Healed ulcer
No. capillaries per patient	8.0 (6.5–9.5)	7.0 (5.3–8.8)	6.0 (3.0–8.0)	7.5 (5.5–8.8)	5.0 (4.3–7.8)	3.0 (2.3–8.0)	5.0 (1.5–5.5)
Convolutions per capillary	1.0 (1.0–1.1)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.1 (1.0–1.4)	2.4 (1.7–3.9)	3.5 (3.1–5.7)	9.0 (7.6–11.3)

Difference between medians: 2.0 capillaries (95% CI: −1–6.0), 7.2 convolutions (95% CI: 5.3–8.8) Wilcoxon.

Conclusions: Amongst patients with venous disease, capillary convolution is strongly associated with the more severe stages (lipodermatosclerosis and healed ulceration). It may be possible to use this measure to assess the efficacy of new treatments for chronic venous insufficiency.

Vascular 005

Preserved nitric oxide synthase content in human saphenous vein graft harvested with its surrounding tissue

J.C.S. Tsui,[1] D.S. R. Souza,[3] D. Filbey,[4] M.R. Dashwood[1,2] and D.M. Baker[1]

Departments of [1]Surgery and [2]Molecular Pathology and Clinical Biochemistry, Royal Free and University College Medical School, London NW3 2QG and Departments of Thoracic and Cardiovascular Surgery[3] and Transfusion Medicine,[4] Orebro Medical Centre Hospital, Sweden

Aims: A novel 'no-touch' technique of saphenous vein (SV) harvesting where the SV is harvested with a cushion of surrounding tissue with no distension has led to improved early patency rates and preserved endothelial integrity and endothelial nitric oxide synthase (NOS). Our aim was to study total NOS distribution and content in segments of SV harvested by this technique.

Methods: Following local ethical committee approval, SV was harvested from 10 patients undergoing coronary artery bypass grafting. A segment of the vein was harvested using the conventional technique (surrounding tissue stripped and vein distended with saline); another segment was stripped but not distended (control) and the remaining parts harvested using the 'no-touch' technique. Samples of each vein segment were taken and slide-mounted sections prepared for histochemistry and autoradiography. NOS was localized using ^{3}[H] L-N^G nitroarginine autoradiography and NADPH-diaphorase histochemistry. Morphometric analysis was carried out to quantify the amount of positive NADPH-diaphorase staining. Endothelial cells and nerves were identified using CD31 and NF200 immunohistochemistry.

Results: Lumenal endothelial NOS was almost-continuous in 'no-touch' and non-distended control segments, whilst on conventional segments it was patchy. NOS was also localized to adventitial vasa vasorum and nerves in 'no-touch' vessels. These were absent where the adventitia was removed. NOS content (corrected for area of section) was reduced by 19.5% in non-distended control veins and by 35.5% in conventional veins compared to 'no-touch' veins ($P < 0.05$, one-way ANOVA, Bonferroni's post test), suggesting that both distension and stripping of perivascular tissue reduce NOS sources.

Conclusions: NOS content is better maintained in SV harvested by the 'no-touch' technique due to preserved adventitial NOS sources as well as endothelial NOS. This may lead to increased NO availability in these grafts where the vasculoprotective properties of NO will contribute to the improved patency rates reported using this technique.

Vascular 006

N-acetyl cysteine attenuates acute muscle injury following compartment syndrome

S.R. Kearns,[1] D. Moneley,[2] C. Condron,[2] P. Murray,[1] C. Kelly[2] and D. Bouchier-Hayes[2]

[1]Department of Orthopaedics, Cappagh Hospital, and [2]Department of Surgery RCSI, Beaumont Hospital, Dublin 9, Ireland

Aims: Compartment syndrome induces a neutrophil mediated tissue injury. Our aim was to evaluate the efficacy of *N*-acetyl cysteine, an anti-oxidant, in the prevention of CS induced acute muscle injury.

Methods: Sprague–Dawley rats ($n = 6$ group^{-1}) were randomized into control, CS and CS pretreated with NAC (0.5 g kg^{-1} i.p. 1 h prior to induction). Cremasteric muscle was isolated on its vascular pedicle and placed in a specially designed plastic chamber. To induce CS chamber pressure was maintained at diastolic 10 mmHg for 3 h. 1 h after decompression muscle function was assessed by electrical field stimulation and peak twitch and maximum tetanic contraction values were recorded. Tissue neutrophil infiltration was assessed by myeloperoxidase activity and tissue oedema by the wet-to-dry ratio.

Results: Compartment syndrome resulted in a significant decrease in muscle twitch and tetanic contraction. CS also resulted in a significant increase in tissue oedema. Pretreatment with NAC attenuated CS induced muscle injury as assessed by these parameters.

	Peak twitch	Maximum tetanus	Wet:dry ratio
Control	202.4 ± 18.6	602.6 ± 52.2	0.84 ± 0.05
Compartment syndrome	59.9 ± 8.3 *	328.5 ± 23.1 *	1.06 ± 0.06†
CS and NAC	120.8 ± 13.9 †	507.1 ± 30.4†	0.89 ± 0.04†

Results = mean ± SEM. * $p < 0.01$ *versus* control; †$p < 0.05$ *versus* I-R (ANOVA). CS, compartment syndrome; MPO, myeloperoxidase; NAC, *N*-acetyl-cysteine.

Conclusions: These data show that administration of the anti-oxidant *N*-acetyl cysteine results in significant attenuation of the muscle injury and oedema caused by compartment syndrome without reducing neutrophil infiltration.

Vascular 007

Homocysteine-induced apoptosis is inhibited by vitamin B_6, B_{12} and folate

T.C.F. Sykes, G. Molostvov,[1] A. Morris[1] and D. Mosquera

Department of Vascular Surgery, Birmingham, and [1]Heartlands Hospital Biological Sciences, University of Warwick, UK

Aims: Previous work has demonstrated that homocysteine (Hcy) induces apoptosis of human vascular endothelium in combination with adenosine, a mechanism that may be important in the pathogenesis of atherosclerosis, for which Hcy has found to be an independent risk factor. The aim of this study was to determine whether vitamins used in Hcy lowering therapy could prevent Hcy-induced apoptosis.

Methods: Human umbilical vein endothelial cells (HUVECs) were coincubated with D,L-Hcy, adenosine, methyltetrahydrofolate (MeTHF), pyridoxal-5-phosphate (B_6), or methylcobalamin (B_{12}) either alone or in combination, for 4 h. Apoptosis was measured by flow cytometry after staining with annexin V and propidium iodide.

Results: Hcy, adenosine, MeTHF, B_6 or B_{12} alone did not induce significant apoptosis compared to control. Hcy-induced apoptosis (Hcy and adenosine) was inhibited by MeTHF, B_6, and B_{12} independently. Maximal inhibition occurred in the presence of all three vitamins.

Apoptosis in HUVECs (mean% ± SD)	4 h
Control	10.3 (3.5)
Hcy (0.5 mM) + adenosine (0.5 mM)	21.6 (5.9)*
Hcy (0.5 mM) + adenosine (0.5 mM) + MeTHF (0.1 mM)	16.5 (9.1)†
Hcy (0.5 mM) + adenosine (0.5 mM) + B_6 (0.1 mM)	12.8 (6.4)†
Hcy (0.5 mM) + adenosine (0.5 mM) + B_{12} (0.1 mM)	9.3 (3.5)†
Hcy (0.5 mM) + adenosine (0.5 mM) + MeTHF + B_6 + B_{12}	7.2 (3.3)†

*$P < 0.01$ *versus* control, †$P < 0.01$ *versus* (Hcy + Ad) ANOVA.

Conclusions: Folate, B_6 and B_{12} inhibit Hcy-induced apoptosis in human vascular endothelium. This may be an important mechanism in attenuating vascular injury associated with hyperhomocysteinaemia.

Vascular 008

Altered endothelin-1 levels in chronic and acute lower limb ischaemia

J C S Tsui[1], N.I. Garlick,[2] M.R Dashwood[1,3] and D M Baker[1]

Departments of [1]Surgery, [2]Orthopaedics and [3]Molecular Pathology and Clinical Biochemistry, Royal Free and University College Medical School, London NW3 2QG, UK

Aims: The vasoconstrictor peptide endothelin-1 (ET-1) has been implicated in the pathophysiology of several cardiovascular conditions. Our aim was to study circulating and tissue levels of ET-1 in chronic and acute lower limb ischaemia.

Methods: Following ethical committee approval, systemic blood and open muscle biopsies were obtained from 8 patients undergoing total knee replacements (TKR) and 6 undergoing lower limb amputations for critical limb ischaemia (CLI), of similar age. Two sets of biopsies were taken from the TKR patients: one prior to tourniquet application (non-ischaemic sample) and one after a period of tourniquet-induced acute ischaemia (acutely ischaemic sample, average tourniquet time one hour). Transverse muscle sections were prepared and ET-1 identified by standard immunohistochemistry using a monoclonal anti-ET-1 antibody. Cells exhibiting positive ET-1 immunostaining were counted within a grid and plasma ET-1 levels measured by ELISA.

Results: Plasma levels of ET-1 were higher in CLI patients compared with those undergoing TKR (mean ± SEM 1.98 ± 1.22 *versus* 0.47 ± 0.20, $P = 0.23$, Mann–Whitney U test). However, there was no change in circulating ET-1 levels during the period of acute ischaemia. At the tissue level, ET-1 immunoreactivity was significantly greater in chronically ischaemic muscle compared with non-ischaemic muscle (32.2 ± 0.60 ± *versus* 9.59 ± 0.31, $P < 0.0001$, Mann–Whitney U test), and almost doubled following acute ischaemia (19.1 ± 0.44 *versus* 9.59 ± 0.31, ($P < 0.0001$, Wilcoxon signed rank test). This suggests that alterations in the ET-1 pathway occur primarily at a tissue level and elevated systemic levels seen in chronic ischaemia are secondary to persistent local peptide production.

Conclusions: Our results show that the ET-1 pathway is involved in both chronic and acute skeletal muscle ischaemia where ET-1 may reduce microvessel tone, exacerbating the ischaemic damage. These changes occur locally, suggesting that the potential therapeutic benefits of ET antagonists may be maximized by targeting the ischaemic tissue directly.

Vascular 009

Primed neutrophils in the venous effluent convert local to systemic inflammation after limb ischaemia–reperfusion injury

A Lewis,[1] D W Harkin,[2] A A.B Barros D'Sa,[2] K McCallion,[1] M I Halliday[1] and F C Campbell[1]

[1]Department of Surgery, The Queen's University of Belfast and the [2]Vascular Surgical Unit, The Royal Victoria Hospital, Belfast, UK

Aims: Priming of neutrophils is a key step in the development of local and systemic injury in ischaemia–reperfusion (I/R). We hypothesized that neutrophil priming in the hind limb on reperfusion would precede systemic inflammation.

Methods: Anaesthetized ventilated swine ($n = 6$ per group) were randomized to control or I/R (bilateral external iliac artery occlusion for 2 h followed by 2.5 h reperfusion) group. Blood was sampled simultaneously over time from the femoral, portal, hepatic and systemic veins, respectively. Bronchoalveolar (BAL) lavage was carried out at the end of the reperfusion period. Using luminol, respiratory burst activity was assayed with a BioOrbit Luminometer to detect whole blood or BAL fluid chemiluminescence (CL) by stimulation with phorbol 1.2-myristate 1.3-acetate (PMA) in the absence or presence of tumour necrosis factor (TNF), respectively, giving a phagocytic cell priming ratio. Plasma bioactive interleukin (IL)-6 indicates systemic inflammation. Alveolar-arterial (A-a) oxygen gradient and mean pulmonary artery pressure (PAP) indicate lung function.

Results: I/R caused significantly greater neutrophil priming after 30 min reperfusion in the femoral vein 1.01 (0.08), compared to systemic, 0.80 (0.03), portal, 0.74 (0.07), and hepatic sites, 0.76 (0.07) ($p < 0.05$). Systemic neutrophil priming was significantly greater at the end of reperfusion in the I/R group, 0.83 (0.14), compared to control group, 0.22 (0.04) ($p < 0.001$). BAL neutrophil priming was not significantly different between control group, 0.82 (0.13), and I/R group, 0.95 (0.07). Plasma IL-6 was significantly increased after I/R, 1616.6 ± 390.8, compared to control, 430.54 ± 66,17 ($P < 0.005$). A-a gradient was significantly increased after I/R 407.97 ± 53.13, compared to control, 183.2 ± 45.8 ($p < 0.005$). PAP was significantly greater after I/R, 42.0 ± 5.0 mmHg, compared with control, 27.9 ± 1.9 mmHg ($P < 0.005$). Data represents mean (standard error mean), comparisons using one-way ANOVA and Student's *t*-test.

Conclusions: Neutrophil priming initiated in the hind limb on reperfusion precedes systemic neutrophil priming, systemic inflammation and acute pulmonary dysfunction.

SRS: Oncology 1–9

Wednesday 25 April 2001 11:00–12:30

Oncology 001

The development of an accurate, reproducible image analysis system to assess microvessel density in solid tumours

C.D. Sutton, J.C. Goddard, P.D. Furness, K.J. O'Byrne,
A.R. Dennison and D.P. Berry
The University Hospitals of Leicester NHS Trust, UK

Aims: To develop a reproducible and accurate image analysis system for the assessment of microvessel density (MVD) in solid tumours that could be duplicated in any surgicopathology unit possessing an image capture facility.
Methods: Two solid tumour models were used, superficial bladder cancer and colorectal liver metastases. Consecutive paraffin sections from a block of each of these cancers were cut and mounted on silane slides. Microvessel were stained using anti-CD34 monoclonal antibody (Novacastra) enhanced with DAB and copper sulphate or nickel sulphate. Slides were exposed to Mayer's haematoxylin, methyl red, methylene blue or light green, for 15, 10, 5 or 1 s. Interpretation was by two investigators. Accurate vessel recognition by eye and image analysis and ability to identify histological architecture was recorded. Images were captured using a JVC KYF50 3-chip colour video camera and a Scion EGF frame grabber attached to an Apple Macintosh G-3 computer. Image analysis was performed using the freeware program NIH Image. Within this software, a macro was written that automatically converted captured coloured images to grey scale and counted the number of individual stained vessels. Using the most suitable staining technique, the variables of threshold level, minimum and maximum particle size recognized and automatic dilation and erosion factors were changed in a systematic fashion until there was 100% accuracy of computer counting compared to manual counting. This macro was then tested by comparison of manual *versus* computer counting in 30 randomly chosen areas in 30 cases of superficial bladder cancer and 30 cases of colonic liver metastases.
Results: Nickel sulphate enhanced CD34 staining with a 1 s exposure to Mayer's haematoxylin was the only combination that allowed successful identification of the histological architecture along with accurate computerized MVD counting.

Manual count *versus* computer count		
Colonic liver metastases	$r = 0.96$	$P = 0.01$*
Superficial bladder cancer	$r = 0.98$	$P = 0.01$*
Manual count *versus* computer count in 30 random areas		
Colonic liver metastases	$r = 0.94$	$P = 0.01$*
Superficial bladder cancer	$r = 0.96$	$P = 0.01$*

*Spearman rank.

Conclusions: Using a combination of appropriate vessel immuno-identification with the described image analysis system an extremely accurate measurement of MVD can be achieved in any laboratory.

Oncology 002

Circulating levels of vascular endothelial growth factor (VEGF) correlate with platelet count and are only transiently affected by surgery

G.M. Spence, A.N.J. Graham, K. Mulholland,[1] I. McAllister,
K.G. McManus, P. Maxwell,[1] J.M. Sloan,[1] M.A. Armstrong,[3]
F.C. Campbell[2] and J.A. McGuigan
Department of Thoracic Surgery, Royal Victoria Hospital, Belfast, and [1]Departments of Pathology,[2]Surgery and [3]Immunobiology, Queen's University, Belfast, BT12 6BJ, UK

Aims: Serum and plasma VEGF levels (S-VEGF, P-VEGF) may have prognostic significance in patients with cancer. Physiological wound healing may also elevate circulating VEGF levels; as such our aim was to investigate the effect of surgery on S-VEGF and P-VEGF and to evaluate their relationship to platelet count, which has a putative role in VEGF transport.
Methods: S-VEGF, P-VEGF and platelet count were measured in 23 patients undergoing oesophagectomy. Samples were taken pre-operatively and at 6 weeks post-operatively. Seven patients were also sampled on post-operative days 1, 5 and 10. VEGF measurement was undertaken by ELISA.
Results: Data are expressed as median (IQR) with statistical analysis by Wilcoxon signed ranks testing. Correlation analysis is by Spearman's rank testing.

	Pre-op ($n = 23$)	Day 1 ($n = 7$)	Day 5 ($n = 7$)	Day 10 ($n = 7$)	6 weeks ($n = 23$)
S-VEGF	250	313	*1017	*1231	365
(pg mL^{-1})	(131–476)	(201–608)	(446–1224)	(626–2046)	(189–634)
P-VEGF	10	*55	64	†58	†20
(pg mL^{-1})	(0–23)	(46–104)	(21–181)	(20–154)	(0–65)
Platelet count	275	†289	346	†399	273
(10^6 L^{-1})	(241–343)	(195–350)	(289–387)	(311–501)	(239–486)

*$P = 0.018$, †$P = 0.028$, †$P = 0.049$ *versus* pre-operative.

Platelet count correlated with S-VEGF and P-VEGF and ($P = 0.021$ and $P = 0.006$, respectively).
Conclusions: Surgery has an effect on both S-VEGF and P-VEGF levels which is transient; as such it should not interfere with the interpretation of circulating VEGF as a prognostic marker outside the early post-operative period. S-VEGF and P-VEGF both correlated with platelet count, providing evidence of an association between platelets and VEGF in the circulation.

Oncology 003

Early breast cancers (EBC) expressing epidermal growth factor receptor (EGFR) have increased parathyroid hormone related protein (PTHrP) expression

R.A. Linforth, N.G. Anderson, F. Knox and N.J. Bundred
Academic Department of Surgery, South Manchester University Hospital, Manchester M20 8LR, UK

Aims: EGFR signalling, which is augmented by breast-related kinase (BRK), increases the production of PTHrP in breast cancer cell lines. We determined the incidence of co-expression of PTHrP, EGFR, BRK and CerbB2 oncoprotein in early breast cancers (EBC).
Methods: Using standard immunohistochemical techniques, the expression of PTHrP, EGFR, BRK and CerbB2 oncoprotein expression was determined on formalin fixed EBC. Disclosure of all primary antibodies was performed with swine anti-rabbit antibody, streptavidin and diaminobenzidine-hydrogen peroxides staining. Positive staining was classed as greater than 5% of epithelia expressing the target antigen. A positive control was used in each run and a control slide used for each test sample. Scoring was performed by a single observer, and verified by an experienced pathologist. Results were analysed using the χ^2 test.
Results:

	EGFR		BRK		CerbB2		
PTHrP	pos	neg	pos	neg	pos	neg	Total
Pos	22*	25	39**	8	16	31	47
Neg	3	20	13	10	9	14	23
Total	25	45	52	18	25	45	70
	*$P = 0.006$		**$P = 0.017$		$P = 0.67$		

Expression of EGFR and BRK were more frequent in those tumours co-expressing PTHrP compared to those which were PTHrP negative ($P = 0.006$ and $P = 0.017$, respectively). In addition PTHrP +/EGFR + EBC were associated with a higher rate of lymph node metastases when compared to PTHrP-/EGFR- (65% *versus* 27% $P = 0.02$).
Conclusions: EGFR and BRK expression in EBC is associated with increased PTHrP expression *in vivo*. Drugs designed to inhibit EGFR signalling may be useful in treating PTHrP induced hypercalcaemia of malignancy and bone metastases.

Oncology 004

HER-2 in node-negative breast carcinoma: prognostic significance

R.S. Rampaul, S.E. Pinder, J.A. Bell, P. Wencyk, D.M. Macmillan,
R.W. Blamey, J.F.R. Robertson and I.O. Ellis
Nottingham City Hospital, Nottingham, UK

Aims: Previous studies have established the prognostic value of HER-2 in patients who are node-positive but the data in still inconclusive in node-negative patients. We have evaluated the prognostic significance of Her-2 over-expression in a large cohort of node-negative breast cancer patients, none of whom received systemic adjuvant therapy.
Methods: Paraffin-embedded node-negative primary breast cancers from 678 patients were studied immunohistochemically using an antibody (DAKO)

raised against the p185 protein. HER-2 (p 185) staining was scored as 0, 1, 2, 3, where 2 and 3 was assessed as positive for over-expression. Univariate analysis was performed with χ^2 tests to compare immunoreactivity with known pathological and patient variables. Cox regression analysis with size and -grade was performed to evaluate HER-2 over-expression as an independent prognostic factor.

Results: Forty per cent (n = 254) of specimens showed over-expression of HER-2. Compared with those in whom HER-2 was not over-expressed, this group had a significantly worse DFI ($P = 0.008$) and overall survival ($P = 0.0044$). A significant relationship was also observed with high grade ($P = 0.00001$), ER negativity ($P = 0.00001$), young age ($P = 0.0276$) and Nottingham Prognostic Index ($P = 0.0003$). No association was observed with menopausal status ($P = 0.43116$), vascular invasion ($P = 0.80447$) or tumour size ($P = 0.5033$). In multivariate analysis for survival, Her-2 showed independent prognostic significance ($P = 0.0002$).

Conclusions: This analysis and previous reports on lymph node-positive disease suggest that HER-2 is an independent adverse prognostic factor irrespective of nodal disease. Her-2 status may provide a means to identify those node-negative patients at increased risk of relapse who should be considered for standard adjuvant systemic therapy and possibly Herceptin.

Oncology 005

The effects of conjugated linoleic acid on the expression of key genes involved in the apoptotic pathway

B Majumder,[1] S. Moir,[1] K J Wahle[2] and S D Heys[1]

[1]Department of Surgery, University of Aberdeen and [2]Rowett Institute, Aberdeen, UK

Aims: The anti-tumour effects of the dietary fatty acid, conjugated linoleic acid (CLA), may be mediated through enhanced apoptosis. However, the effects of CLA on genes involved in apoptosis are unknown and this study examines the effects of CLA on p53, p21WAF1 and bcl-2 expression in addition to the cytotoxic effects of CLA on breast tumour growth.

Methods: Oestrogen receptor positive and negative breast cancer cells (MCF7, MDA-MBA-231) were grown in supplemented RPMI media, containing CLA at concentrations (0μM to 200μM) for 24 h. The effects on cell growth were assessed using MTT assay. Following treatment with CLA, Northern blotting was performed to determine the effects on the expression of p53, p21 WAF1 and bcl-2. All experiments were carried out in triplicate.

Results: Exposure to CLA resulted in a dose -dependent reduction in growth of MCF-7 cells – 20% at 6.25 μM, 50% at 100 μM and 65% at 200 μM ($P < 0.001$). Similar results were obtained for MDA-MBA-231 cells. Northern blot analysis showed that CLA treatment caused a dose dependent increase in wild-type p53 expression (MCF-7 cells) by 284% at 12.5 μM, 347% at 100 μM, and 523% at 200 μM of CLA ($P < 0.01$). There was no change in bcl-2 expression. The expression of p21 WAF1, a key downstream regulator of p53, was raised to 203%. CLA did not change the expression of mutant p53 (present in MDA-MBA-231 cells) or p21 WAF1, but did increase the expression of bcl-2 by 103% at 12.5 μM, 201% at 50 μM, and 207% at 100 μM of CLA ($P < 0.01$).

Conclusions: This is the first demonstration that CLA may cause its anti-tumour effects by increasing the expression of the wild-type p53 and the p21 WAF1 gene. However, in cells with mutant p53, CLA inhibits cells growth, through a p53-independent pathway.

Oncology 006

Influence of irradiation on matrix metalloproteinase expression and activation

W J Speake, R Asher Dean, H.M. Collins, A Kumar, J H Scholefield and S A Watson

Academic Unit of Cancer Studies, Academic Unit of Surgery, University Hospital Nottingham, Nottingham NG7 2UH, UK

Background: Evidence has suggested that irradiation increases matrix metalloproteinase (MMP) expression and activation in rectal cancer to a greater level than in normal rectal mucosa. The aim of this study was to evaluate the temporal expression of MMPs in a positive control tumour cell line, HT1080 (fibrosarcoma known to express MMP-2 and MMP-9) following irradiation alone and co-cultured with human fibroblasts.

Methods: HT1080 cells were exposed to irradiation at a level of 4 Gray alone, and in co-culture with the human fibroblast cell line, 46Br1G1. Flow cytometry following propidium iodide staining confirmed the position of cells within the cell cycle. Messenger RNA expression was quantified by real time polymerase chain reaction using the SYBR green dye. Protein expression was confirmed by zymography and semi-quantified using image analysis.

Results: Irradiation of HT1080 resulted in cell cycle arrest. Temporal gene expression of both MMP-9 and MMP-2 showed significant increases at 24 h after irradiation ($P < 0.01$ and $P < 0.05$, respectively) which returned to baseline levels by 96 h. This resulted in increased pro-MMP-9 expression (163% at 24 h, 128% at 48 h, $P < 0.05$) and increased pro-MMP-2 expression (165% at 48 h, $P < 0.05$). However with co-culture of HT1080 and 46Br1G1 there was a significant increase ($P < 0.05$) in MMP-2 and 9 at the gene and protein levels and increased activation of MMP-2. No significant increase in MMP expression was observed when 46Br1G1 was irradiated alone.

Conclusions: Recovery from irradiation leads to a concurrent increase in MMP production of the MMP-expressing fibrosarcoma positive control cell line but not the fibroblastic line, however, the presence of the fibroblasts were required for maximal activation of MMP-2.

Oncology 007

Anti-angiogenic therapy attenuates micrometastatic tumour growth in a Lewis lung carcinoma model

K K Austin, J Wang, K C Redmond, S Sookhai, W O Kirwan and H P Redmond

Cork University Hospital, Wilton, Cork, Ireland

Introduction: While surgery results in successful removal of the primary tumour in the majority of patients, a significant number of patients subsequently die of metastatic disease despite chemotherapy. The mechanism for this may relate to the stimulation of dormant micrometastases by surgically-induced proangiogenic factor release. We hypothesized that use of anti-angiogenic treatment may attenuate micrometastatic tumour growth.

Methods: C57BL/6 mice were inoculated via tail vein injection with 5×10^5 3LL-122A cells. Controls received IgG MoAb (10 μg i.p.) at 24 h, then every 3 days for 14 days post inoculation. The treatment group also received anti-VEGF MoAb (10ug i.p.) at the same timepoints. Animals were sacrificed at day 14 post inoculation and their lungs were removed. Quantitative analysis of the number of micrometastases was performed after serial sectioning and haematoxylin and eosin staining by an independent assessor using digital image analysing microscopy at an objective field of 20. Statistical analysis with ANOVA was used.

Results: Control mice demonstrated a mean metastatic score of 115 ± 31. Mice who received anti-VEGF MoAb had significantly attenuated micrometastatic tumour growth (25.5 ± 8 $P = 0.03$).

Conclusions: This study demonstrates that the administration of anti-VEGF mAb therapy significantly attenuates micrometastatic tumour growth when compared to controls in a Lewis lung carcinoma murine model. Further studies in patients with solid tumours are warranted to evaluate the role of anti-VEGF therapy on micrometastatic tumour growth in the proangiogenic perioperative period.

Oncology 008

Gene therapy for pancreatic cancer; combination of cytotoxic agents with adenoviral-delivered tumour-suppressor genes increases cytopathic effect

C M Halloran, P Ghaneh, P. Costello and J P Neoptolemos

Department of Surgery, Royal Liverpool University Hospital, 5th Floor UCD Building, Daulby Street, Liverpool L69 3GA, UK

Aims: To investigate the combined effects of adenoviral mediated over expression of the tumour suppresser genes p16 (Adp16) and p53 (Adp53) with either, 5-flurouracil (5-FU) or gemcitabine, in pancreatic adenocarcinoma cell lines.

Methods: Pancreatic adenocarcinoma cell lines were incubated with the above cytotoxic drugs, either at supra or sub LD-50 doses, before or after inoculation with Adp16 or Adp53 or a control adenoviral vector containing the luciferase gene (AdLuc), with multiplicities of infection (MOIs) of 10-100. The cell viability was assessed 5 days post-treatment using an MTT assay.

Results: High-dose combinations of 5FU with either Adp16 or Adp53, decreased cell survival compared to relevant controls, by 50–60%. However, enhanced cytopathic effect was observed with low dose combinations of the cytotoxic agents with either Adp16 or Adp53, cell survival decreased compared to 'relevant controls, by 55% for 5FU + p16, 70% for gemcitabine + p16, all with additive effect, synergistic effect being seen with Adp16 combinations ($P < 0.05$).

Conclusions: Combining cytotoxic agents with either Adp16 or Adp53 significantly reduces survival of pancreatic adenocarcinoma cell lines. When doses of drug and MOIs of virus that are individually, relatively ineffective, are used in this combination, the resultant reduction in cell number is pronounced.

Oncology 009

Reduction in thrombospondin 1 expression significantly correlates with disease progression in superficial bladder cancer

J.C. Goddard, C.D. Sutton, J.L. Jones, D.P. Berry, K.J. O'Byrne and R.C. Kockelbergh

The University Hospitals of Leicester NHS Trust, UK

Aims: Decreased expression of thrombospondin-1 (TSP-1) has been shown to be associated with decreased survival and disease recurrence in invasive bladder cancer. The purpose of this study was to investigate the relationship of TSP-1 expression in a series of superficial bladder cancers.

Methods: A series of 108 cases of superficial bladder cancer were chosen at random. Cases were included if the archived paraffin-embedded specimen from the first resection was available and excluded if follow-up was less than 12 months and if the disease was found to be invasive at the 3 month check cystoscopy. Immunohistochemical staining was performed with Ab-4 an antibody to TSP-1 (Neomarkers). Antigen retrieval was achieved by predigestion with Pronase E (1 mg mL^{-1}) (Sigma) for 15 min at 37°C and developing was with the EnVision-DAB system (Dako). The staining was quantified in conjunction with a consultant histopathologist (LJ). A scoring system was developed and applied to all cases The results were entered into a computerised database upon which statistical analysis was performed using SPSS version 10.

Results: Of the 108 cases, 55 progressed to muscle invasive disease and 53 did not. Immuno-staining of TSP-1 was discrete and confined to four distinct areas: epidermal-stromal junctional, perivascular, tumour cell, stromal. The percentage staining for each of the areas and the total staining score is displayed in the table (results shown as mean (range)).

	Percentage of staining				
	Epidermal-stromal	Perivascular	Tumour cell	Stromal	Staining score
Progression	3 (0–40)	4 (0–30)	0	1 (0–20)	6 (4–20)
Non-progression	7 (0–70)	8 (0–50)	1 (0–5)	2 (0–80)	8 (4–20)
Mann–Whitney	0.029	0.005	0.075	0.113	0.001

SRS: Sepsis/General 1–9

Wednesday 25 April 2001 11:00–12:30

Sepsis/General 001

Macrophages which have ingested apoptotic neutrophils promote resolution of inflammation by regulating tissue repair, angiogenesis and leukocyte infiltration

C Power, J Wang, J Street, S Sookhai and H P Redmond

Department of Academic Surgery, Cork University Hospital, Cork, Ireland

Aims: Macrophage (MØ) ingestion of apoptotic neutrophils (PMN) is crucial to resolution of inflammation. We investigated the production of matrix metalloproteinase-9 (MMP-9), Tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and vascular endothelial growth factor (VEGF) by MØ had had phagocytosed apoptotic PMN and how these same MØ promote further MØ recruitment and phagocytosis of apoptotic PMN through tight regulation of the chemokines interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1)
Methods: MØ were cultured from 7 to 10-day-old monocytes PMN apoptosis was induced by UV light MMP-9, TIMP-1, VEGF, I -8, MCP-1 release from activated MØ which had ingested apoptotic PMN and control MØ was measured by ELISA Leukocyte chemotaxis was assessed using human umbilical vein endothelium-plated Transwells and monoclonal antibodies against IL-8 and MCP-1.
Results: MØ which had ingested apoptotic PMN promoted monocyte chemotaxis ($P<0.05$) at the expense of PMN Results of cytokine production are expressed as percentage of control $P<0.05$* ANOVA

	MMP-9 (ng mL^{-1})	TIMP-1 (ng mL^{-1})	VEGF (pg mL^{-1})	IL-8 (pg mL^{-1})	MCP-1 (ng mL^{-1})
Control MØ	100%	100%	100%	100%	100%
MØ+PMN	75±5%*	154±9%*	148±12%*	46±17%*	107±9%

Conclusions: MØ that have ingested apoptotic PMN decrease MMP-9 production and increase TIMP-1 and VEGF, limiting tissue damage and encouraging angiogenesis and repair. PMN influx is actively suppressed by limiting IL-8 release, whereas MØ recruitment is encouraged by maintaining MCP-1 levels This reduces PMN mediated cytotoxicity and enhances phagocytosis of offending PMN thereby helping to resolve inflammation

Sepsis/General 002

Inhibition of inflammatory signal transduction in bacterial lipoprotein (BLP) tolerized human monocytes

M. Doyle, J H Wang, B Manning, Q D Wu and H P Redmond

Department of Academic Surgery, Cork University Hospital, University College Cork, Cork, Ireland

Aims: Both endotoxin/Lipopolysaccharide (LPS) tolerance and BLP tolerance represent an essential control mechanism during sepsis. We have previously demonstrated that BLP tolerance is superior to LPS tolerance in protecting against septic shock-induced mortality, however, the underlying mechanisms involved in BLP tolerance are not clear. In this study, we investigated the alterations in inflammatory signal transduction pathways following BLP tolerance
Methods: BLP tolerance and LPS tolerance in human THP-1 monocytic cells were induced in either serum-present or serum-free culture system to evaluate the involvement of soluble CD14 Tolerized cells were further stimulated with high doses of BLP or LPS TNF-α and IL-6 levels were determined by ELISA. Toll-like receptor 2 (Tlr 2), mitogen-activated protein kinases (MAPK), including ERK, JNK, and P38 kinase were detected by western blotting NF-kB activation was assessed by transfection of the pNFkB-Luciferase reporter vector and electrophoretic mobility shift assay (EMSA). A number of MAPK and NF-kB inhibitors were also used to determine which signal pathway was involved in BLP tolerance
Results: BLP-tolerized monocytes had a significant reduction in TNF-α production in response to high doses of BLP (41±9 pg mL^{-1} *versus* 2341±537 pg mL^{-1} in nontolerized cells, $P<0.01$), or LPS (30±7.5 pg mL^{-1} *versus* 1001±147 pg mL^{-1} in nontolerized cells, $P<0.01$). Using a specific CD14 blocking mAb and a serum-free culture system revealed that induction of BLP tolerance was independent of both membrane CD14 and soluble CD14. BLP tolerance as well as LPS tolerance inhibited phosphorylation of ERK, JNK, and p38 kinase, and activation of NF-kB in response to subsequent BLP or LPS stimulation There was a marked downregulation of Tlr 2 expression in BLP tolerized cells, whereas LPS tolerance did not affect Tlr 2 expression

Conclusions: These results indicate that LPS+BLP tolerance share similar intracellular mechanisms. The critical difference between each peptide relates to differential expression of Tlr 2 amd Tlr 4

Sepsis/General 003

Unfractionated heparin attenuates lipopolysaccharide-induced neutrophil activation

B J Manning, J H Wang and H P Redmond

Department of Academic Surgery, Cork University Hospital, Cork, Ireland

Aims: Heparin has anti-inflammatory actions, and has been shown to benefit patients with acute exacerbations of inflammatory bowel disease, and to improve outcome when used in experimental models of sepsis. We aimed to determine the effect of unfractionated heparin (UH) on polymorphonuclear neutrophil (PMN) activation in response to lipopolysaccharide (LPS)
Methods: Human PMNs (1×10^6 cells mL^{-1}) isolated from healthy volunteers were incubated for 2 h, at 37° and 5% CO_2, in culture medium with and without the addition of UH (100 units mL^{-1}), LPS (100 ng mL^{-1}) or LPS+UH (100 ng mL^{-1}) CD11b and CD18 expression were determined by flow cytometry after incubation with fluorescently labelled monoclonal antibodies (mAb) To determine the extent, if any, of heparin binding to PMNs, cells were incubated with biotinated heparin and subsequently treated with streptavidin R-phycoerthrin The percentage of cells to which heparin bound was determined by comparing mean channel fluorescence (MCF) cell^{-1} with and without the presence of heparin, and the pretreatment of cells with anti-CD11b mAb, anti-CD18 mAb or both, was used to evaluate the role of these integrins in heparin binding Results are MCF cell^{-1} ± SE (ANOVA)
Results: LPS upregulated PMN expression of CD11b from 242±44 to 579±72 ($P<0.05$), and this effect was blocked by coincubation with UH 287±44 ($P<0.05$) CD18 expression (215.2±78) was up-regulated by LPS (426±67, $P<0.05$), and this was also attenuated by UH (196±41 $P<0.05$) Heparin was found to bind to 10.2±1.5% of PMNs CD11b blocking mAb reduced this to 5.0±0.8%, and CD18 mAb reduced this to 4.3±0.8%.
Conclusions: Heparin significantly attenuates LPS induced PMN activation, by preventing up-regulation of CD11b and CD18 following its binding to these receptors These findings may, in part, explain the anti-inflammatory effect seen *in vivo*.

Sepsis/General 004

Nuclear factor-κB (NF-κB activation is required for endotoxin-induced tumour cell adhesion and invasion

B J. Manning, J H Wang, Q D. Wu and H P Redmond

Department of Academic Surgery, Cork University Hospital, University College Cork, Cork, Ireland

Aims: Endotoxin/lipopolysaccharide (LPS) promotes tumour growth and metastasis We have previously shown that LPS has direct effect on tumour cell attachment to and invasion into extracellular matrix proteins by upregulation of β1 integrin expression This study was designed to test the hypothesis that endotoxin-induced tumour cell adhesion and invasion are dependent on NF-kB activation
Methods: Human colorectal tumour cell lines SW480 and SW620 were treated with LPS (0.1 μg mL^{-1}) or LPS plus recombinant soluble CD14 (rsCD14, 0.2 μg mL^{-1}), in the presence of the NF-κB inhibitor SN50 (100 μg mL^{-1}) β1 integrin expression was detected by flow cytometry NF-κB activation was assessed by transfection of the luciferase reporter pNFκB-Luc vector, and further confirmed by electrophoretic mobility shift (EMSA) assay Tumour cell adhesion and *in-vitro* tumour cell invasion through Matrigel chambers were assessed
Results:

			LPS+ rsCD14+	
	Medium	LPS alone	LPS+ rsCD14	SN50
β1 integrin (MCF cell^{-1})	103±14	117±12	217±23*	132±22†
Adhesion (%)	14±3.7	14±3.9	43±11*	20±4.4†
Invasion (numbers)	19±6.1	20±4.9	62±9.2*	24±5.7†

Data = mean ± SD, $n=6$, Stats ANOVA, *$P<0.05$ *versus* medium and LPS alone, †$P<0.05$ *versus* LPS+ rsCD14

LPS alone did not activate NF-kB. However, LPS in the presence of rsCD14 resulted in NF-kB activation in both SW480 and SW620 cells as demonstrated by transfection and EMSA. Pretreatment of SW480 and SW620 cells with the NF-kB inhibitor SN50 significantly attenuated LPS plus rsCD14 induced up-regulation of β1, α2, α3, α6 expression. Furthermore, SN50 prevented LPS plus rsCD14 induced tumour cell adhesion and invasion.

Conclusions: These results indicate that endotoxin mediated β1 integrin over-expression, and subsequent increased tumour cell adhesion and invasion requires NF-kB activation.

Sepsis/General 005

Bacterial wall products enhance tumour cell production of interleukin 6 and vascular endothelial growth factor through nuclear factor-κB (NF-κB)-dependent and -independent pathways

M. Doyle, J.H. Wang and H.P. Redmond

Department of Academic Surgery, Cork University Hospital, Ireland

Background: Tumour cells have previously been shown to produce interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) and both cytokines can also promote tumour growth and metastatic potential. We have previously shown that bacterial wall products, bacterial lipoprotein (BLP) and endotoxin (LPS) enhance tumour growth. It was our aim to determine if BLP and LPS increase IL-6 and VEGF production from tumour cells and to evaluate some of the mechanisms involved in this process.

Methods: SW 480 human colorectal carcinoma cells were incubated with BLP (100–1000 ng mL^{-1}), LPS (100–1000 ng mL^{-1}) and LPS + BLP (100–1000 ng mL^{-1}) for 12 and 24 h. Supernatants were assayed for IL-6 and VEGF using standard immunosorbant assay. In some experiments the NF-κB inhibitor, SN50, was added 30 min prior to stimulation with LPS and BLP. NF-κB was measured by transfection of the p NF-κB luciferase reporter vector.

Results: Analysis of variance was used for statistical analysis.

Cytokine (pg mL^{-1})	Medium	BLP	LPS	LPS + BLP	BLP + SN50	LPS + SN50	LPS + BLP + SN50
IL-6	467 ± 30	^689 ± 25	^990 ± 23	^1132 ± 98	*409 ± 16	*502 ± 25	*516 ± 26
VEGF	489 ± 48	^763 ± 81	^934 ± 86	^1131 ± 98	875 ± 53	1048 ± 91	1409 ± 109

^*versus* medium treated cells. **versus* no NF-κB inhibition. $P = 0.0001$.

BLP and LPS both increase IL-6 and VEGF production and NF-κB activation from SW480 cells. IL-6 but not VEGF, production is suppressed by inhibiting NF-κB.

Conclusion: Bacterial wall products stimulate tumour production of IL-6 and VEGF. IL-6, but not VEGF production, is NF-κB dependent.

Sepsis/General 006

Increased capsaicin receptor VR1-immunoreactivity in acute inflammatory bowel disease

C.L.H. Chan,[1,3] Y. Yiangou,[1] P. Facer,[1] N.H.C. Dyer,[2]
C.H. Knowles,[1,3] N.S. Williams[3] and P. Anand[1]

[1]*The Peripheral Neuropatny Unit, Imperial College School of Medicine, Hammersmith Hospital, London, UK.* [2]*Neurobiology Unit, Roche Bioscience, Palo Alto, California, USA, and Academic Department of Surgery, Barts and the* [3]*London School Medicine and Dentistry, UK*

Aims: Abdominal pain, discomfort and urgency are characteristic symptoms of acute inflammatory bowel disease (IBD). Capsaicin, the main pungent ingredient of 'hot' chilli peppers, elicits the sensation of burning pain and discomfort by selectively activating sensory neurons. The aim of this study was to investigate whether there was increased expression of the cloned capsaicin receptor (VR1) in acute IBD.

Methods: Macroscopically involved, histologically confirmed inflamed colon was collected at time of colectomy from patients with Crohn's disease ($n = 6$) or ulcerative pancolitis ($n = 3$). Abdominal pain was a predominant symptom in all but one patient. The specimens were studied by immunohistochemistry and by western blotting using antibodies to VR1. Control colonic tissue was obtained from eight patients undergoing similar resections from nonobstructing carcinoma.

Results: Western blotting revealed an eight-fold increase in relative optical density in the IBD group compared with the control group ($P < 0.01$). In normal colon, only weak submucosal labelling of VR1 fascicles was detected. However, in the IBD group, moderate to strong immunostaining was observed in numerous nerve fascicles.

Conclusion: Our data demonstrates for the first time the presence of VR1 in normal human colonic tissue. In addition, we have shown that there is increased VR1 expression in colonic nerve fibres in acute IBD. Thus, the discovery of novel drugs or naturally occurring substances that can bind the VR1 receptor may lead to new therapies for pain and dysmotility that is seen in acute IBD.

Sepsis/General 007

Rapamycin has no effect on established allograft vasculopathy

G.J. Murphy, G.R. Bicknell, R.N. Saunders, M.S. Metcalfe and M.L. Nicholson

Division of Transplant Surgery, University Department of Surgery, Leicester General Hospital, UK

Aims: Progressive allograft vasculopthy and organ fibrosis (chronic rejection) remains an important cause of late organ transplant failure and no therapeutic agent has been shown to have an effect on this process. Rapamycin is a novel immunosuppressant that has been shown to inhibit intimal hyperplasia and fibrosis in animal models but to date the effect of rapamycin on established allograft vasculopathy in humans or animal models remains unclear. The aim of this study was to measure the effects of rapamycin on established allograft vasculopathy as well as to measure its effect on the expression of genes that control extracellular matrix turnover in established chronic rejection.

Methods: Thoracic aortas from F344 rats were transplanted heterotopically into the abdominal aorta of Lewis recipients. Six animals per group started rapamycin (0.5 mg kg^{-1} day^{-1}) at 8, 12, and 16 weeks with six receiving no treatment as a control. Grafts were harvested at 24 weeks and analysed histologically. mRNA was extracted from frozen tissue and expression of fibrosis associated genes was studied by means of quantitative reverse transcriptase-polymerase chain reaction.

Results: Between eight and 24 weeks untreated allografts developed significant intimal thickening and expansive vascular remodelling. Levels of gene expression for species important in extracellular matrix remodelling are listed below. Values are expressed as a ratio of the house keeping gene β Actin.

		Rapamycin commencement			
	8 weeks	12 weeks	16 weeks	Control	*P* value
Intimal medial ratio	0.13 ± 0.22	0.18 ± 0.06	0.16 ± 0.1	0.26 ± 0.22	0.925
MMP 2	2.4 ± 0.48	2.05 ± 1.18	2.23 ± 0.47	2.83 ± 0.20	0.27
MMP 9	3.83 ± 0.97	4.62 ± 1.45	3.76 ± 1.47	4.25 ± 0.7	0.38
TIMP 1	1.58 ± 0.20	1.99 ± 0.53	1.45 ± 0.22	1.42 ± 0.06	0.13†
TIMP 2	2.35 ± 0.35	2.35 ± 0.21	2.20 ± 0.50	2.52 ± 0.23	0.49
Collagen 3	2.11 ± 0.25	2.69 ± 0.82	2.02 ± 0.39	1.80 ± 0.12	0.17†
TGF β	3.74 ± 0.54	2.97 ± 1.53	3.40 ± 0.29	3.57 ± 0.30	0.46

Mean values ± St. deviation, P = Kruskall–Wallis. †Collagen 3, Timp 1 significantly higher in 12 week group by Mann–Whitney.

Conclusions: These data suggest that Rapamycin has no significant effect on allograft vasculopathy and may in fact increase pro-fibrotic gene expression in allografts with early allograft vasculopathy.

Sepsis/General 008

Integrins in the adhesion of human colonic fibroblasts to matrix components

C.C.W. Mahon, F.J. Savage and P.B. Boulos

Academic Department of Surgery, University College London, UK

Aims: Cell–matrix interactions mediated by integrins may be important in fibroblast adhesion, migration and proliferation during colonic healing. The aim of this study was to define the integrins required for adhesion of human colonic fibroblasts to collagen I, a major constituent of normal matrix, and to fibronectin an important component of wound provisional matrix.

Methods: Human colonic fibroblast cultures were obtained from digested colonic mucosa. Cell suspensions (4×10^5 cells mL^{-1}) were incubated in the presence or absence of antibody to the integrins α1, α2, α3, α4, α5 or β_1, before adding 4×10^4 cells well^{-1} to microtitre plates coated with collagen I or fibronectin. After incubation for 1 h nonadherent cells were removed by washing. Adherent cells were fixed and quantified by a methylene blue assay. The results are expressed as median absorbance in arbitrary units for test wells (in the presence of antibody) A_{Ab} and controls A_c. Statistical analysis is by the Wilcoxon signed rank test.

Results: Adhesion to collagen was inhibited by antibody to the β_1 integrin subunit, $A_{Ab} = 0.08$, $A_c = 0.98$ ($n = 20$, $P < 0.0001$) and by antibody to the α_1 integrin subunit, $A_{Ab} = 0.02$, $A_c = 0.78$ ($n = 9$, $P = 0.0039$). Adhesion to fibronectin was partially inhibited by antibody to the β_1 subunit, $A_{Ab} = 0.83$, $A_c = 1.06$ ($n = 13$, $P = 0\ 0097$) and by antibody to α_5, absorbance $A_{Ab} = 1.06$, $A_c = 1.21$ ($n = 9$, $P < 0\ 0039$). No significant inhibition of adhesion to collagen or fibronectin was observed in the presence of antibodies to the α2, α3, or α4 integrins

Conclusions: The major determinant of adhesion of human colonic fibroblasts to collagen 1 is the $\alpha_1\beta_1$ integrin. Only partial inhibition of adhesion of colonic fibroblasts to fibronectin could be achieved using antibodies to α_5 or β_1 suggesting that other cell adhesion molecules are involved in this interaction.

Sepsis/General 009

Retinal pigment epithelial cells which have phagocytosed preoxidized photoreceptor outer segments express chemotactic and angiogenic cytokines

G T Higgins, J H Wang, P E. Cleary and H.P. Redmond

Department Ophthalmology/Department Acad Surgery, University College Cork, Ireland

Aims: Retinal pigment epithelial (RPE) cells accumulate lipofuscin pigment as a result of oxidative alternations in phagocytosed photoreceptor outer segments (POS) Accumulation of lipofuscin is thought to be related to age-related macular degeneration (AMD). We evaluated the effect of phagocytosis of UV-irradiated POS (artificial lipofuscin) on the expression by RPE on the expression of various chemotactic and angiogenic cytokines

Methods: ARPE-19 cells were exposed to latex beads (0 8 μm), bovine POS and UV-irradiated POS (OX) ($2 \times 10^7\ mL^{-1}$) and supernatants were collected at 6, 18 and 36 h. The supernatants were assayed for IL-8, MCP-1 and TNFα by ELISA. Protein synthesis and NFκB activity were inhibited by actinomycin D and SN50, respectively. Phagocytosis and generation of reactive oxygen species (ROS) was assessed by flow cytometry The effects of the supernatants on proliferation of a human microvascular endothelial cell line were assessed using a BrdU cell proliferation ELISA.

Results: IL-8 and MCP-1 expression was decreased in the POS group (IL-8 473 76 ± 66 9 $P = 0.0005$; MCP-1. 550 1 ± 21 8, $P = 0\ 0001$), but increased in the OX group (IL-8 1348 8 ± 164.9, MCP-1 1772 28 ± 65.19) compared with control (IL-8· 741 09 ± 39 8, MCP-1: 1413 47 ± 38.4) and latex beads TNFα levels were not affected At 12 h after challenge ROS were induced in the oxidized POS group The cytokine increases observed were dependent on *de novo* protein synthesis and were partially NFκB dependent.

Conclusions: Ingestion by RPE of oxidized bovine POS stimulates production of chemotactic and angiogenic cytokines, which may promote angiogenesis directly, or through the accumulation of immune cells such as monocytes which themselves may cause angiogenesis This may be of significance in the development of exudative AMD

SRS: Patey Prize 9–16 Wednesday 25 April 2001 13:30–15:30

Patey Prize 009

Flutamide suppresses VEGF expression in the HaP-T1 Syrian hamster model of advanced pancreatic cancer

A.T. Abraham, S.R. Shah, Y. Sirivatanauksorn and B.R. Davidson

Royal Free & University College School of Medicine, London, UK

Aims: To study the effect of the anti-androgen flutamide on tumour growth and spread in the HaP-T1 Syrian hamster model of advanced pancreatic cancer and determine if the effect is mediated by suppression of vascular endothelial growth factor (VEGF) expression.

Methods: Flutamide (30 mg kg^{-1} day^{-1} s.c.) was administered 5 weeks after implantation of HaP-T1 pancreatic adenocarcinoma in Syrian hamsters ($n=12$). Controls ($n=12$) were injected with vehicle. The extent and pattern of local progression and distant spread was assessed at necropsy 14 days later. Tumour tissue was harvested for histopathology. Levels of VEGF mRNA expression in frozen pancreatic tumour tissues were determined by semiquantitative RT-PCR.

Results: Treatment with flutamide decreased the mean ± SE tumour weight ($1.3+0.4$ g *versus* 2.9 ± 1.1 g, $P=0.19$). The number of animals with evidence of metastases was also lower in the flutamide group (six *versus* three, $P=0.4$). Levels of VEGF mRNA were significantly lower in pancreatic tumours in the flutamide-treated group (0.27 ± 0.04 *versus* 0.46 ± 0.06, $P=0.03$). VEGF mRNA levels were higher in pancreatic tumours of animals with metastatic spread (0.47 ± 0.05 *versus* 0.26 ± 0.05, $P=0.01$). Tumour weight correlated strongly with VEGF expression in the control group ($r=0.75$, $P=0.03$). No such correlation was seen in the in the flutamide-treated group ($r=0.09$, $P=0.92$).

Conclusions: Flutamide suppresses pancreatic tumour VEGF mRNA expression in advanced pancreatic cancer in the HaP-T1 Syrian hamster model. This may explain its effect as adjuvant therapy in the palliation of advanced pancreatic cancer in humans.

Patey Prize 010

Regional variation of microvascular abnormalities in patients with peripheral arterial disease is related to disease distribution

A. Abidia, G. Kuhan, H. Bahia, I. Chetter and P.T. McCollum

Department of Vascular Surgery, Academic Surgical Unit, RHHT and The University of Hull, Hull HU3 2JZ, UK

Aims: Abnormal microvascular reflexes precede the development of peripheral arterial disease, however, regional variation and the role of such abnormalities in dictating the distribution of arterial disease are less clear. We aimed to compare the microvascular response to thermal stimulation in the upper limb with the lower limb in patients with established peripheral arterial disease.

Methods: Twenty patients with peripheral arterial disease (PAD) and five normal controls (NC) were recruited for this study. Laser Doppler flux was measured over the forearm and the forefoot of all patients and controls before and after heating the probes to 44°C.

Results: The mean increase in laser Doppler flux response to thermal stimulation was 621% in the forefoot and 1077% in the forearm in PAD group ($P=0.034$, Man-Whitney) compared with 1580% and 1749%, respectively, in NC group. Furthermore, the difference in the response to thermal stimulation between the two groups in the forefoot was significant ($P=0.015$, Mann–Whitney) while the forearm responses were not.

Conclusion: Microvascular response to thermal stimulation was significantly diminished in the lower limbs of patients with arterial disease compared with their upper limbs and with normal controls. Regional variation in these abnormalities may play an important role in the predisposition to and distribution of arterial disease.

Patey Prize 011

The effects of a selective cyclo-oxygenase-2 inhibitor on colonic anastomotic and wound healing strengths

R.A. Cahill, E. Kavanagh, G. McGreal and H.P. Redmond

Department of Academic Surgery, Cork University Hospital, N. U. I. (Cork), Wilton, Cork, Ireland

Background: Selective inhibitors of the inducible form of cyclo-oxygenase (COX-2) are of potential benefit in the perioperative period for both their analgesic and, perhaps, antineoplastic actions. However, the effects of these drugs on intestinal wound healing are unknown.

Methods: Forty adult Sprague–Dawley rats (mean weight 358.4 g, range 300–455) underwent laparotomy, descending colonic transection and handsewn re-anastomosis, having been randomized to receive either a selective COX-2 inhibitor (rofecoxib, 10 mg kg^{-1}) or an equal volume of water by gavage preoperatively and then daily postoperatively. Animals were killed either 3 or 7 days later (10 rats per group at each time point) and their wounds evaluated using tensiometry (skin and colonic wounds) and bursting pressure measurement (colonic anastomoses).

Results: While all rats in the control group convalesced uneventfully, five animals receiving rofecoxib had anastomotic leaks by day 7 ($P<0.05$, χ^2 test). Intact colonic suture lines were also significantly weaker in this group(both bursting pressures ($P<0.05$) and tensile strengths ($P<0.05$) (Mann–Whitney) at both time points. Skin wound strengths were similar in each group (see tables, values are mean ± standard error).

Table 1 Colonic anastomoses

	Tensile strength (n mm^{-1})		Bursting pressure (mmHg)	
Group	Day 3	Day 7	Day 3	Day 7
Control	0.8 ± 0.1	1.3 ± 0.2	62 ± 11	181 ± 16
Rofecoxib	0.6 ± 0.1	0.8 ± 0.3	29 ± 7	73 ± 37

Table 2 Skin wounds

	Tensile strength (n mm^{-1})	
Group	Day 3	Day 7
Control	4.3 ± 0.7	3.5 ± 0.3
Rofecoxib	3.7 ± 1.0	2.5 ± 0.3

Conclusions: Although beneficial in the treatment of pathological inflammation, our results strongly suggest that selective COX-2 inhibitors may adversely affect colonic anastomotic healing.

Patey Prize 012

Mapping the intracellular pathway by which dopamine (DO) induces neutrophil (PMN) apoptosis and the identification of PMN-bound dopamine receptors

C. Power, J. Wang, S. Sookhai, M. Carr and H.P. Redmond

Dept. of Academic Surgery, Cork University Hospital, Cork, Ireland

Aims: We have demonstrated that dopamine induces PMN apoptosis, which may partly explain the beneficial effects of DO administration to septic patients. Herein we investigate whether PMN express DO receptors (D_{1-5}) and the effects of DO on PMN mitochondrial depolarisation (mΩ), intracellular calcium flux [Ca] and caspase-3, all recognized regulators of apoptosis.

Methods: DO was used in 10+100 umolar doses. PMN apoptosis was assessed using propidium iodide staining and mean channel fluorescence (MCF) flow cytometry at 4 hly timepoints. In control and test PMN, the parameters mΩ, [Ca] and caspase-3 protein expression were measured using the chromophore JC-1, calcium-specific probe Fura-2 and Western immunoblotting, respectively. DO receptors were studied using polyclonal antibodies and immunohistochemistry.

Results: We identified three DO receptors, $D_{1,2,5}$ on PMN.

	4-h control	8-h control	12-h control
% Apoptosis	10 ± 2	22 ± 6	39 ± 8
mΩ (MCF)	943 ± 42	723 ± 15	678 ± 22
[Ca] (MCF)	83 ± 3	96 ± 5	132 ± 8
	4-h DO	8-h DO	12-h DO
% Apoptosis	14 ± 9	34 ± 7*	57 ± 6*
mΩ (MCF)	808 ± 17*	450 ± 43*	378 ± 61*
[Ca] (MCF)	90 ± 3*	100 ± 3*	162 ± 10*

DO induces increased PMN caspase-3 expression as demonstrated on Western blotting.

Conclusions: DO induction of PMN apoptosis is associated with significant increases in mΩ and [Ca], which translates into pro-apoptotic activity as evidenced by pronounced Caspase-3 protein expression. These original findings and the identification of DO receptors on PMN indicate that DO induces profound anti-inflammatory activity within PMN's most probably through these newly identified PMN receptors.

Patey Prize 013

Severe acute pancreatitis is associated with increased systemic nitric oxide: evidence implicating an endotoxin-mediated response

S.H. Rahman, B.J. Ammori, G. Barclay, I.G. Martin, M. Larvin and M.J. McMahon

Academic Unit of Surgery, The General Infirmary, Great George Street, Leeds LS1 3EX and The National Transfusion Science Laboratories, Edinburgh, UK. Tel: 0113 3923462; fax: 0113 3923635

Aims: To assess if systemic nitric oxide production is elevated in patients with severe acute pancreatitis (SAP) and whether this is in part due to an endotoxin-mediated response.

Methods: Patients with a clinical and biochemical diagnosis of AP were studied within 72 h of onset of abdominal pain. The 24-h NO-derived urinary nitrite excretion was measured using the Greiss reaction. The ratio of renal excretion of the enterally administered polyethylene glycol (PEG) 3350/400 was measured to determine intestinal macromolecular permeability. The IgM:IgG EndoCAb ratio was used as a marker of systemic endotoxin exposure. Attacks were classified as mild or severe according to the Atlanta criteria.

Results: Sixty-five patients with AP (severe 20) and 20 healthy control subjects were studied. Urinary nitrite excretion was significantly increased in patients with severe attacks (median 20.6) compared to mild attacks (median 15.7, $P = 0.003$), and the latter was significantly greater in healthy controls (median 6.3, $P = 0.004$). PEG excretion ratios were significantly increased in patients with severe attacks compared to mild attacks ($r = 0.8$, $P < 0.01$). In patients with severe disease, urine nitrite excretion demonstrated a positive and significant correlation with intestinal macromolecular permeability and the IgM:IgG EndoCAb ratio ($r = 0.7$, $P = 0.006$, and $r = 0.8$, $P = 0.001$, respectively).

Conclusion: Systemic NO is increased in AP, and is greatest amongst patients who develop a severe attack. The strong correlation with altered gut permeability and endotoxin exposure suggests that the mechanism may be mediated through bacterial upregulation of inducible nitric oxide synthase activity.

Patey Prize 014

Synergistic effect of endostatin and etoposide inhibition in endothelial progenitor cell proliferation

G.F. Nash, M.F. Scully[1] and A.K. Kakkar

Imperial College School of Medicine, London Thrombosis Research Institute, London, UK[1]

Aims: The effects of angiogenesis inhibitor endostatin and the mitosis inhibiting agent etoposide were investigated upon endothelial progenitor cells (EPCs), and compared to mature human vascular endothelial cells (HUVECs). The recently described EPCs, that are found to circulate in adult blood, have been shown to localize at foci of angiogenesis *in vivo*.

Methods: EPCs were isolated by Ficoll gradient purification of blood bank buffy coat. The resulting cells, which immunostained positively for CD31 and CD34, were grown in Medium 199, on fibronectin-coated plates. HUVECs were cultured from fresh umbilical cord vein. The effects of recombinant human endostatin and etoposide were studied at increasing concentrations over 7 days of culture. MTS (a tetrazolium salt) cell proliferation assay was performed to establish the effects on cell proliferation, each experiment being repeated four times.

Results: Endostatin at a dose of 0.5 µM inhibited EPC proliferation by 28%, but HUVEC proliferation by only 11% ($P < 0.05$). When 0.5 µM endostatin was combined with etoposide at a dose of 12 µg mL^{-1}, there was a 54% inhibition of EPC proliferation compared to a 19% inhibition with etoposide alone ($P = 0.001$).

Conclusions: These data indicate that mature endothelial cells are less sensitive to the effect of endostatin than EPCs, which display a proangiogenic phenotype *in vitro*, and are thus a superior model to test antiangiogenic therapies. The additive effects of antiangiogenic and chemotherapeutic agents upon EPCs suggest important clinical anti-cancer effects may result from such combination therapies.

Patey Prize 015

Pravastatin, a HMG-COA reductase inhibitor, improves flow-mediated dilation in young insulin-dependent diabetics

M. Joyce, C.J. Kelly, K. Moore, C. Thompson, P. Fitzgerald, A. Leahy and D.J. Bouchier-Hayes

Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland

Aims: Young insulin-dependent diabetics (IDDM) exhibit impairment of flow-mediated dilatation, a nitric oxide dependent phenomenon. Emerging evidence suggests that statins, independent of their serum lipid lowering properties, have beneficial effects on endothelial function. We hypothesize that 1-month treatment with pravastatin, would restore to normal, flow-mediated dilation in young IDDM.

Methods: Flow-mediated dilation of the brachial artery was measured using high-resolution ultrasonography. Diabetics were compared with age matched non-diabetic controls. The diabetic group were given pravastatin, 40 mg per day for 1 month at the end of which time brachial artery reactivity was reassessed.

Results:

		Diabetics	
	Controls	Pre-treatment	Post-treatment
Baseline vessel diameter (mm)	4.04 (0.25)	4.73 (0.23)	4.37 (0.22)
Flow-mediated dilation (%)	7.98 (1.1)	4.5 (0.31)*	8.44 (0.9)#

Data are expressed as mean (SEM). Analysis with ANOVA, *post hoc* Scheffé test. * $P < 0.05$ *versus* controls. # $P < 0.05$ *versus* diabetic pre-treatment group.

Conclusions: These data confirm the presence of significant endothelial dysfunction in young insulin dependent diabetics. One month of pravastatin treatment restored endothelial dependent dilatation to that of control values.

Patey Prize 016

26S proteasome inhibition overcomes NF-κB-induced chemoresistance in human pancreatic cancer

S.A. Shah, M.W. Potter, R.D. Kim, R.S. Chari and M.P. Callery

Dept. of Surgery, University of Massachusetts Medical School, USA

Apoptosis induced by conventional chemotherapeutic agents may be limited by their co-activation of NF-κB-dependant anti-apoptotic genes. We have reported that stabilisation of the NF-κB inhibitor, IκBα, by proteasome inhibition promotes tumour apoptosis. These studies examined whether NF-κB blockade by specific 26S proteasome inhibition (PS-341) could enhance the tumouricidal effects of CPT-11 in pancreatic cancer, a highly chemoresistant tumour.

Methods: Quiescent human pancreatic cancer cells (BxPC3, PANC-1) were stimulated to proliferate (10% FCS) ±10 nM PS-341, 5 µM CPT-11 or both. Proliferation was determined by MTT assay, and IκBα by Western blot. To evaluate anti-tumour effects *in vivo*, subcutaneous BxPC3 tumour xenografts were established (50 mm^3) in athymic nu/nu mice ($n = 40$). Next, animals received either vehicle, single agent (CPT-11 *or* PS-341), or combined agent (CPT-11 and PS-341) therapy. Tumour volumes and body weights were measured biweekly. 40 days later, tumours were harvested and analysed for apoptosis (TUNRL), cellular proliferation (*in vivo* BrDU), and NF-κB activation (EMSA). Statistical analysis – ANOVA ($P < 0.05$).

Results: *In vitro*, CPT-11 significantly blocked FCS-induced proliferation in both cell lines only when combined with PS-341. Degradation induced by CPT-11 alone (15 min) was prevented in cells also treated with the 26S proteasome inhibitor. *In vivo*, CPT-11 alone limited tumour growth by 43%. Combination therapy with PS-341 enhanced this tumour sensitivity to CPT-11 (89%) without apparent toxicity ($P < 0.01$). Combined CPT-11/PS-341 therapy, but not single agent therapy, yielded highly apoptotic tumours, significantly inhibited tumour cell proliferation, and blocked NF-κB activation, indicating this systemic therapy was effective at the cancer cell level.

Conclusions: 26S proteasome inhibition enhances the tumouricidal effects of CPT-11 chemotherapy in human pancreatic cancer by stabilising IκBα and preventing NF-κB activation. This is the first demonstration that NF-κB-dependent chemoresistance may be overcome in pancreatic cancer.

P, 25, 318

SRS: Upper Gastrointestinal 1-6 — Wednesday 25 April 2001 16:00–17:00

UGI 001

L-N^6-(1-Iminoethyl)-lysine decreases severity of acute pancreatitis and associated haemodynamic changes

K. Ayub, R.C.N. Williamson and R.T. Mathie

Imperial College School of Medicine, Hammersmith Hospital Campus, London, UK

Aims: To determine whether treatment with the iNOS inhibitor L-N^6-(1-iminoethyl)-lysine (L-NIL) decreases severity of experimental acute pancreatitis and its associated haemodynamic changes.
Methods: Sixty-min ischaemia and 6-h reperfusion of the pancreas was induced in male Wistar rats by temporary occlusion of the four main pancreatic arteries (inferior pancreatico-duodenal artery, splenic artery, left gastric artery, gastroduodenal artery), either without or with additional administration of L-NIL (group B and group C, respectively, n = 10 each). Data were compared with those of corresponding sham-operated controls (group A, n = 10). Continuous data were analysed using ANOVA with contrasts to define specific inter-group differences and are expressed as mean ± SEM. Categorical data were analysed using Fisher's exact test.
Results: Group B animals displayed reduced mean arterial blood pressure (79.0 ± 6.1 mmHg) compared with group A (95.5 ± 2.4; $P = <0.01$). Treatment with L-NIL (group C) corrected the reduction in blood pressure (95.0 ± 2.9; $P < 0.01$) compared to group B. Pancreatic injury (macroscopic changes, histological scoring, pancreatic wet:dry ratio and serum amylase) was markedly reduced in group C rats compared with those in group B.
Conclusions: Inhibition of iNOS by L-NIL ameliorates acute pancreatitis and associated haemodynamic abnormalities in this rat model. NO generated by iNOS plays an important mediator in the pathogenesis of acute pancreatitis.

UGI 002

The effect of inhibition of nitric oxide synthase using MEG on the outcome of severe acute pancreatitis

R.A. Al-Mufti, R.C.N. Williamson and R.T. Mathie

Division of Surgery, Anaesthetics & Intensive Care, Hammersmith Hospital, Imperial College School of Medicine, London, UK

Background and aims: The role of nitric oxide (NO), overproduced by the inducible NO synthase (iNOS), has been established as a key inflammatory mediator in the systemic inflammatory response leading to the multiple organ dysfunction syndrome. The aim of this study was to examine the effect of treatment with the selective iNOS inhibitor mercaptoethylguanidine (MEG), which also acts as a scavenger of cytotoxic and free radical species, on the course of severe acute pancreatitis in the rat.
Methods: Acute severe necrotising pancreatitis was induced in 10 adult male Wistar rats by a combination of biliopancreatic duct infusion of glycodeoxycholic acid and arterial infusion of caerulein. Data were compared to those in sham operated controls ($n = 10$). The effect of MEG treatment was examined in a disease group ($n = 10$) and in a control group ($n = 10$). MEG was administered 2 h after induction of pancreatitis. At 7 h blood pressure, PaO_2, and serum creatinine were measured. Pancreatic sections were examined histologically and morphometric measurement of areas of acinar cell necrosis as a percentage of total acinar tissue area was performed.
Results: Compared with controls at 7 h, the pancreatitis group displayed reduced mean arterial blood pressure [mean (SEM) 77.8 (3.7) *versus* 108.2 (2.2) mmHg, $P < 0.0001$], reduced PaO_2 [66.7 (1.9) *versus* 115.2 (3.6) mmHg, $P < 0.0001$], and raised serum creatinine [132.5 (20.6) *versus* 41.8 (2.5) µmol L^{-1}, $P < 0.0001$]. Treatment with MEG corrected the reduction in blood pressure [mean (SEM) 112.2 (3) mmHg, $P < 0.0001$], and ameliorated the reduction of PaO_2 levels [89.4 (2.2) mmHg, $P < 0.0001$] and the rise in serum creatinine [66.8 (3.7) µmol L^{-1}, $P = 0.012$]. There was reduction in morphometric measurement of areas of acinar necrosis as a percentage of total acinar tissue in histological sections in the treated group compared with pancreatitis [16.84 (0.84) *versus* 39.66 (1.47)%, $P < 0.0001$].
Conclusions: In this experimental model of severe acute pancreatitis, treatment with MEG two hours after induction of pancreatitis corrected circulatory failure, ameliorated renal and respiratory functions, and limited the progression of pancreatic necrosis. MEG may prove to have a useful role in the supportive treatment of multiple organ failure and in limiting pancreatic necrosis in a severe attack.

UGI 003

T-cell activation following acute pancreatitis: an antigenic effect

K.J. Sweeney, M.R. Kell, T. Murphy and J.V. Reynolds

Department of Clinical Surgery, St James's Hospital, Dublin, Ireland

Aims: Acute pancreatitis is associated with a systemic inflammatory state. The underlying immunological mechanisms are unclear. This study investigated the effect of pancreatitis on T-cell activation.
Methods: Peripheral blood samples of 12 patients with acute pancreatitis were taken 24 h, 48 h, and 7 days following initial presentation. CD3+ T-cell activation was detected by expression of CD69 and CD25 by flow cytometric methods. Thereafter, healthy volunteer peripheral blood mononuclear cells (PBMCs) were incubated for 18 h with serum from pancreatitis patients in the presence and absence of CTLA 4 Ig, a potent inhibitor of antigen presentation.
Results: The percentage of CD3+ T-cells expressing CD25 and CD69 was significantly increased 24 h following admission (median (range), 41% (21–50) and 24% (7–40), respectively, $P < 0.05$ *versus* controls). There was no significant reduction in expression of CD25 or CD69 in the following week ($P > 0.03$). Pancreatitis serum activated normal T-cells. However in the presence of CTLA 4 T-cell activation did not occur (table).

Healthy volunteer PBMCs incubated with	24 h serum	48 h serum	7 day serum
Serum alone	2.4 (0.5)	7.2 (2.7)	4.6 (1.7)
Serum and CTLA 4	1.6 (0.3)*	1.9 (0.5)*	2.2 (0.6)

Mean percentage CD3+ T-cells expressing CD69 (SEM) *$P < 0.05$ *versus* serum alone.

Conclusions: Acute pancreatitis results in systemic activation of T-cells. This phenomenon is driven by a serum-derived antigen and is a sustained response. Our data suggests that T-cells may play an important role in the pathogenesis of the systemic inflammatory response following acute pancreatitis.

UGI 004

Nuclear factor-κB and heat shock factor 1 are systemically activated in human acute pancreatitis

A.D. O'Reilly, J.R. Roberts, A.G. Demaine and A.N. Kingsnorth

Departments of Surgery and Molecular Medicine, Derriford Hospital, Plymouth, UK

Aims: Nuclear factor-κB (NF-κB) is a transcription factor for a wide range of proinflammatory mediators whilst heat shock factor 1 (HSF-1) transcribes stress proteins that protect against cellular damage. We sought to evaluate the role of these transcription factors in human acute pancreatitis and their relationship to cytokine/chemokine production, disease severity and outcome.
Methods: Among 24 patients with acute pancreatitis and 12 healthy controls, NF-κB and HSF-1 (from nuclear extracts of peripheral blood mononuclear cells) were measured by electrophoretic mobility shift assay and soluble TNF receptors and Interleukin-8 were measured by ELISA. Acute physiology scores (APS), APACHE II scores and final Atlanta designations of severity were determined.
Results: NF-κB and HSF-1 levels were elevated in acute pancreatitis compared to healthy controls ($P = 0.003$ and 0.04, respectively). On simple linear regression, HSF-1 was inversely correlated with APS and APACHE II scores and a final designation (Atlanta) of severe pancreatitis ($P = 0.01$, 0.02 and 0.03, respectively).
Conclusions: Both NF-κB and HSF-1 are systemically activated in human acute pancreatitis. HSF-1 activation appears to protect against severity of pancreatitis.

UGI 005

Tissue-engineered intestine: assessment of morphology and enterocyte dynamics

A. Tavakkolizadeh, A.E Stephen,[1–3] S Kaihara,[3] D L Mooney, B S Kim, S W Ashley, J P Vacanti[2] and E E. Whang[3] (Sponsoring member: Professor N S Williams

[1]*Specialist Registrar in Surgery, West Suffolk Hospital, Bury St Edmonds, UK, Departments of Surgery,* [2]*Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, USA, and* [3]*Department of Chemical Engineering, University of Michigan, Ann Arbor, USA*

Aims: Tissue-engineering techniques have been utilized to generate a prototype neointestine. The aim of this study was to characterize the morphology and topography of enterocyte proliferation and apoptosis in the neomucosa of the tissue-engineered intestine

Methods: Biodegradable polymers seeded with neonatal rat intestinal organoid units were implanted in adult rats to form neointestinal cysts. Five weeks after implantation, five of the rats underwent a side-to-side cyst-jejunal anastomosis. All rats were killed at 6 months. Morphology, epithelial cell proliferation (Br-dU immunohistochemistry) and apoptotic rates (TUNEL assay) were assessed for native jejunal (Jej) and non-anastomosed (N-N) and anastomosed (A-N) neointestinal tissues. Groups were compared using anova.

Results: A-N neomucosa consisted of folds resembling native jejunal crypts and villi, whereas N-N neomucosa was poorly developed. The anastomosis was patent in 80% of the rats at 6 months.

	Mucosal thickness (µm)	Muscularis thickness (µm)	Br-dU rate (%)	Apoptic rate (%)
Jej	551.4 ± 12.5	117.0 ± 5.3	47.3 ± 2.7	0.87 ± 0.23
N-N	102.5 ± 83.7*	537.9 ± 171.8*	32.1 ± 16.2	0.46 ± 0.46
A-N	538.9 ± 95.7 #	358.2 ± 34.0 *	60.5 ± 4.7 #	0.77 ± 0.18

*$P < 0.05$ compared to Jej, #$P < 0.05$ compared to N-N

Neomucosal epithelial proliferation was confined to the lower third of the folds. Apoptosis was evenly distributed throughout the epithelium

Conclusions: These results suggest that the tissue-engineered neomucosa can regenerate structural and dynamic features of the normal jejunum. Anastomosis to the native intestine is an essential step for the development of the neomucosa. Tissue engineering may represent a novel approach to the treatment of patients suffering from short bowel syndrome

UGI 006

Characterization of classical and desmosomal cadherins in the neo-squamous epithelium following ablation of Barrett's oesophagus

C.D. Morris, C. Tselepis, R. Harrison, D. Garrodd, J A Jankowski and S.E.A Attwood

Department of Surgery, Hope Hospital, Manchester and Department of Medicine, Institute of Cancer Studies, Birmingham, UK

Introduction: Endoscopic mucosal ablation with the formation of a 'neo'-squamous epithelium is believed to reduce the risk of adenocarcinoma development in Barrett's oesophagus. However this 'neo' epithelium has not been investigated to prove its similarity to normal squamous epithelium.

Aims: Dysregulation and inappropriate expression of cell adhesion molecules is known to be important in the development of neoplasia, and this study characterizes the expression and function of these molecules in the neo-squamous epithelium

Methods: The expression and cellular localisation of E-cadherin, P-cadherin, β-catenin, γ-catenin and the desmosomal cadherins Dsc1, Dsc2, Dsc3, Dsg1, Dsg2 and Dsg3 in the neo-squamous epithelium were established by immunohistochemistry on serial sections from endoscopic biopsies taken from 10 patients following endoscopic ablation of Barrett's metaplasia and compared to normal squamous epithelium. Levels of expression were confirmed by western blotting, and the ability of each of the cadherins to bind β-catenin and γ-catenin were assessed by co-immunoprecipitation.

Results: Membranous staining for E-cad was seen throughout the 'neo'-squamous epithelium particularly in the basal layers, while P-cad was confined to the basal layers only. Membranous γ-catenin was seen throughout the epithelium. β-catenin was strongly expressed in the basal layers, decreasing towards the lumen. Dsc3, Dsg2 and Dsg3 were maximally expressed in the basal half of the epithelium, decreasing towards the surface, while Dsc2 and Dsg1 were seen mainly in the mid-sections of all cases, with no staining in the basal layers and again gradually decreasing towards the lumen. Dsc1 was absent throughout. All staining patterns were identical to that seen in normal squamous controls and Western blotting studies confirmed similar expression in both 'neo' and normal squamous epithelia. Co-immunoprecipitation of both 'neo' and normal squamous epithelia with β-catenin revealed binding to E- and P-cadherin only, while similar studies using γ-catenin showed binding to classical and all desmosomal cadherins present.

Conclusions: The neo-squamous epithelium formed after endoscopic ablation of Barrett's oesophagus is identical to normal squamous epithelium in both the expression and function of classical and desmosomal cadherins. This data would support the use of ablative therapies in the prevention of adenocarcinoma in Barrett's oesophagus.

SRS: Vascular 10–18 Wednesday 25 April 2001 16:00–17:30

Vascular 010

Chlamydia pneumoniae in carotid atherosclerotic plaques. Innocent bystander?

M.M. Sabetai, T.J. Tegos, J. Coker, B.J. Thomas,[1] M. Sheppard,[2] G. Stansby and A.N. Nicolaides
Department of Vascular Surgery, [1]Department of GU Medicine and Communicable Diseases, Imperial College School of Medicine at St Mary's Hospital, [2]Department of Cardiovascular Pathology, Imperial College School of Medicine at the NHLI/Royal Brompton Hospital, London, UK

Aims: It has been suggested that the presence of *Chlamydia pneumoniae* in atherosderotic tissue may be related to plaque instability and the triggering of clinical events. The aim of this study was to identify any association between the presence of *C. pneumoniae* in carotid plaques and 1) ipsilateral symptomatology; 2) degree of stenosis; and 3) necrotic core volume.
Methods: Seventy-three carotid plaques causing 70–99% stenosis by duplex were removed en-bloc during carotid endarterectomy. Of those, 45 were related to symptoms (11 to amaurosis fugax-AF, 20 to transient ischaemic attacks-TIAs and 14 to stroke) and 28 were asymptomatic. Nested polymerase chain reaction (PCR) was used to detect the presence of chlamydial DNA and computerised planimetry to quantify the necrotic core volume. The latter was expressed as a percentage of plaque volume.
Results: PCR revealed the presence of chlamydial DNA in 26/73 (35%) carotid plaques. The prevalence in symptomatic plaques was 14/26 (54%) and in asymptomatic ones was 12/28 (46% ($\chi^2 = 1.5$, d.f. = 1, $P = 0.2$). Within the symptomatic group there was a higher prevalence of chlamydial DNA 1) in plaques associated with stroke (8/14, 57%) and TIAs (5/20, 36%) than in those associated with AF (1/11, 7%) ($\chi^2 = 7.3$, d.f. = 2, $P = 0.03$) and 2) in those causing higher degrees of stenosis (90% *versus* 85%, $P = 0.05$)*. Within the asymptomatic group there was a higher prevalence in plaques having a larger necrotic core (21% *versus* 12%, $P = 0.05$). Student's t-test.
Conclusions: Our study shows that 35% of carotid plaques contained *C. pneumoniae*. Although there was no significant difference in the presence of chlamydial DNA between symptomatic and asymptomatic plaques, within the symptomatic group the presence of *C. pneumoniae* was significantly higher in severely stenotic plaques and in those associated with cerebral ischaemia (TIAs and stroke) and notably reduced in those associated with retinal ischaemia (AF). Within the asymptomatic group there was a significantly higher prevalence in plaques with a larger necrotic core. These findings highlight the differences between plaques associated with retinal and cerebral ischaemia and may have implications for the pharmacological stabilisation of plaques.

Vascular 011

Tissue-engineering of a novel poly(carbonate-urea) urethane vascular graft MyoLink®

B. Krijgsman, H.J. Salacinski, G. Punshon, A.M. Seifalian and G. Hamilton
University Department of Surgery, Royal Free and University College Medical School, UCL, UK

Aims: We report the first use of a chemically unique compliant poly (carbonate-urea) urethane (MyoLink®) in the tissue engineering of a hybrid vascular graft (HMK). The engineered graft has hierarchical arterial structure: monolayer oriented micro-vascular endothelial cells (MVEC): three-dimensional matrix (human collagen type IV/dermatan sulfate) bonded by dry heat treatment onto MyoLink® (an innovative elastic honeycomb basement layer). The grafts clinical potential was evaluated by determining optimal MVEC seeding density, incubation time, viability and adhesion of these cells when exposed to arterial shear stress.
Methods: MVEC from human omentum were isolated by a new centrifugation protocol, radio-labelled and seeded onto HMK a) $2–18 \times 10^5$ cells cm^{-2} 24 h, b) 1–5 h at 6×10^5 cells cm^{-2}, washed three times and gamma counted. Qualitative assessment of seeding density/incubation was also undertaken with scanning electron microscopy (SEM) and viability tested with Alamar Blue assay. A pulsatile flow phantom was used to subject HMK (200 mm, 5 mm i.d.) seeded with radio-labelled MVEC (6×10^5 cells cm^{-2} at 2 h) to arterial shear and dynamic scintigraphy images acquired in real time using a nuclear medicine gamma camera system during 14th perfusion ($n = 6$).
Results: The optimal seeding density was 6×10^5 cells cm^{-2} and qualitative SEM confirmed this. Incubating cells for 2 h produced significantly greater cell attachment than was seen for 1h incubation ($P < 0.05$) and there was no significant difference in adhesion between cells incubated over the 2 h. Exposure of grafts to acute shear stress resulted in significantly higher proportions of initial cells attached to HMK grafts compared to MyoLink® grafts (67 ± 3% *versus* 55 ± 2%, $P < 0.001$).
Conclusions: As shown here tissue engineering of native MyoLink® significantly augments its surface characteristics by reducing the seeding density and incubation time to produce a mono-layer onto which cells adhere better.

Vascular 012

Do pathogens impair healing in leg ulcers?

A. Bhowmick, S. Kairsingh, D. Ellison and C.N. McCollum
South Manchester University Hospitals Trust, UK

Aims: Antibiotics are frequently prescribed for non-healing leg ulcers without any evidence of efficacy. We compared slow-release clarithromycin with placebo in a randomized clinical trial in 59 leg ulcers that cultured pathogenic bacteria and failed to heal despite 3 months' compression therapy.
Methods: Bacteriological swabs and wound biopsies were cultured in non-healing ulcers with ankle/brachial pressure index >0.6. Patients growing a pathogen on biopsy were randomized to either clarithromycin 500 mg daily or identical placebo given over four weeks. Ulcer size was measured weekly for 8 weeks and wound bacteriology re-investigated by swab and biopsy at weeks 5 and 8.
Results: Median ulcer size (IQ range) was 9.5 cm^2 (4.4–41.7) for the 30 randomized to clarithromycin and 18 cm^2 (7.8–36.2) for 29 on placebo (NS). In 24 of 29 on placebo and 20 of 30 on clarithromycin, staphylococcal/streptococcal infection was detected. Clarithromycin achieved 78% eradication of sensitive organisms within 5 weeks compared with 33% on placebo ($P = 0.01$). Ulcer area reduced by 12.82% for Clarithromycin and 16.47% for placebo at week 5 ($P = 0.74$) and 11.04 and 24.26, respectively, by week 8 ($P = 0.35$). Seven of 30 on clarithromycin and six of 29 on placebo had a reduction in ulcer area of at least 50% at week 5 (NS).
Conclusion: Prolonged antibiotic therapy reduced pathogenic infection of ulcer tissue but had no influence on ulcer healing.

Vascular 013

Hydroxyethyl starch reduces endothelial activation in infrarenal aneurysm surgery

D. Rittoo, P. Gosling, S. Burnley, C. Bonnici, P. Millns, M.H. Simms, S.R.G. Smith and R.K. Vohra
Selly Oak Hospital, University Hospital Birmingham NHS Trust, UK

Aims: To investigate whether hydroxyethyl starch (HES) can stabilize the endothelium activated by ischaemia-reperfusion injury.
Methods: Forty patients undergoing infrarenal abdominal aortic aneurysm surgery were randomly allocated to receive either HES or gelatine as plasma expander. Urinary microalbumin, expressed as the albumin creatinine ratio (ACR), was measured at various timepoints as an index of the systemic capillary leak. The plasma von Willebrand factor (vWf) was also measured at the same time points as an indicator of endothelial activation. The results were analysed using the Mann–Whitney test.
Results: The ACR and the plasma vWf were comparable preoperatively. After aortic clamp release, the systemic capillary leak was significantly greater in the gelatine treated patients (23.3 mg mmol *versus* 9.3 mg mmol^{-1}, $P = 0.03$). This difference persisted up to 4 h after reperfusion (8.6 mg mmol^{-1} *versus* 1.9 mg mmol^{-1}, $P = 0.007$). Although the plasma vWf was comparable immediately following reperfusion of the extremities (96.5% *versus* 110%, $P = 0.3$), it was significantly lower in the patients treated with HES in the perioperative period (80.5% *versus* 173.5%, $P = 0.007$; 82.5% *versus* 160%, $P = 0.01$; 100% *versus* 191%, $P = 0.003$ at 4, 8 and 12 h, respectively, following reperfusion). The plasma vWf remained significantly elevated in the gelatine treated patients (209% *versus* 81%, $P = 0.0004$) even after the systemic capillary leak has returned back to baseline levels.
Conclusions: Compared with gelatine, volume expansion with HES reduces endothelial activation in the perioperative phase of infrarenal aneurysm surgery.

Vascular 014

Self-examination: a novel concept in the detection of aortic aneurysm

I C Chetter, G Kuhan, A.F Abidia, J Bryce, P Renwick,
B Johnson, A R. Wilkinson and P T McCollum
Academic Vascular Unit, Hull Royal Infirmary, Hull, UK

Aims: This study aims to assess the sensitivity, specificity, positive and negative predictive value of self examination in the diagnosis of abdominal aortic aneurysm (AAA)
Methods: Over a 12-month period all patients attending for AAA surveillance or surgery were shown how to examine themselves for an AAA 30 patients attending for carotid duplex were used as controls
Results:

	Small AAA (<4 cm)	Medium AAA (4–5 cm)	Large AAA (>5 cm)
n	22	27	54
Median age (range), years	66 (48–88)	71 (56–89)	76 (59–88)
F M ratio	3 19	4 23	3 51
Median AAA diameter (range), cm	3 4 (2 7–3 9)	4 5 (4 0–5 0)	5 8 (5 10–18 0)
Sensitivity	0 45	0 96	0 93
Specificity	0 73	0 73	0 73
Positive predictive value	0 56	0 76	0 86
Negative predictive value	0 65	0 96	0 85

Conclusions: Self-examination is relatively reliable in detecting AAA over 4 cm in diameter

Vascular 015

Antioxidant depletion during and after AAA surgery

L Wolowczyk, A Day[1], F C.T Smith, R N Baird and P M Lamont
Departments of Surgery and Biochemistry[1], Bristol Royal Infirmary, Bristol, UK

Aims: Antioxidants provide the first line defence against oxygen-derived free radicals generated during ischaemia–reperfusion injury resulting from aortic clamping and clamp release The aim of this study is to evaluate intra- and post-operative antioxidant status in patients undergoing aortic surgery
Methods: Serum total antioxidant capacity (TAC) was measured in venous blood samples taken peri-operatively from 18 patients undergoing elective open infra-renal abdominal aortic aneurysm (AAA) repair
Results:

TAC mmol L^{-1}	Pre-op	Pre-clamp	During clamp	Post-clamp release		
Median	1 17*	0 93	0 74	0 83		
Range	(0 95–1 32)	(0 61–1 13)	(0 31–1 05)	(0 65–1 11)		
	1 h post-op	6 h post-op	12 h post-op	24 h post-op	3 days post-op	7 days post-op
Median	0 83	0 85	0 87	0 87	0 93	0 94
Range	(0 62–1 23)	(0 50–1 19)	(0 72–1 36)	(0 72–1 14)	(0 81–1 20)	(0 82–1 27)

* significantly higher than all other samples ($P<0\ 01$, Wilcoxon signed rank test)

Conclusions: Antioxidant levels during AAA repair start decreasing before aortic clamping, achieve minimum values during aortic clamping and persist low for up to a week post-operatively, possibly reflecting the catabolic phase of recovery.

Vascular 016

Inflammatory response to exercise in claudicants

S Dimitri, L de Cossart, G Mitchel, A Roberts, K Sykes,
G Cottorrell and P R Edwards
Countess of Chester Hospital, University College Chester, UK

Aims: Analysis of blood and urinary inflammatory markers in patients with intermittent claudication (IC)
Methods: Urinary and blood samples were collected prior to and following exercise to maximum walking distance (MWD) in 24 patients. Parameters measured were, brachial blood pressure (BP), heart rate (HR), ankle brachial pressure index (ABPI), interleukin-6 (IL-6), c-reactive protein (CRP), lipids, lactate, urinary microalbuminuria (UMCA), urinary albumin-creatinine ratio (ACR) and relative limb flow (RLF). IL-6 and CRP were also measured at 4 and 5 h post-exercise
Results: Twenty-four patients were tested 19 males, mean age 65 6 ± 7.33 years and five females, mean age 68.2 ± 5.85 years Nine patients were smokers, 11 ex-smokers and four non-smokers Significant parameters are shown in the table

	Pre-exercise		Post-exercise		
Parameter Mean	SE	Mean	SE		*P*-value
IL-6*	3 0	0 00	8 8	1 74	<0 003
CRP*	7 3	0 38	9 8	0 44	<0 0001
UMCA	21 8	5 71	58 0	11 48	<0 001
ACR	4 1	1 26	9 5	2 43	<0 01
Lactate	1 8	0 27	3 6	0 38	<0 001
Systolic ABP	162 0	5 70	180 1	6 45	<0 0001
ABPI	0 8	0 51	0 4	0 49	<0 0001
RLF	0 5	0 71	1 9	0 30	<0 0001

IL-6* and CRP* 4 h post-exercise

The only correlation between inflammatory markers and either the MWD or the ABPI was IL-6 (5 h) [$P<0\ 04$, $r=0\ 41$]
Conclusions: Urinary and blood inflammatory markers increased significantly post-exercise There is a possible association between Il-6 and MWD

Vascular 017

Does pressure gradient guided angioplasty improve angioplasty outcome?

P F S Chong, A Mitchell, N Barratt, M Ellis, L C Brown,
A H Davies, R M Greenhalgh and J. Golledge
Department of Surgery, Imperial College School of Medicine, Charing Cross Hospital, London, UK

Aims: The outcome for angioplasty has been shown to be predicted by the 24- h ABPI measurement However, a peri-procedural technique to predict outcome would potentially allow modification of the procedure to optimize the angioplasty Such a technique may be assessment of the intra-arterial pressure gradient across the flow-limiting lesion to be angioplastied
Methods: Comparison of pressure gradient guided angioplasty (PG-PTA) and conventional angioplasty (C-PTA) was done in a prospective study of 110 limbs undergoing angioplasty In PG-PTA, where possible, the translesional pressure gradient was corrected to 10 mmHg or less by angioplasty or stenting In C-PTA, the quality of angioplasty was judged by completion angiography Haemodynamic success was defined as an increase in ABPI by at least +0 15 following angioplasty and symptomatic success was defined as an improvement of at least one grade according to SVS/ISCVS guidelines Life-table analysis was performed for haemodynamic and symptomatic success
Results: There were no significant base-line differences between the two groups with respect to smoking (0.04) diabetes (0 12), hypertension (0 72), hyperlipidaemia (0 54), ischaemic heart disease (0 22) and cerebrovascular disease (0 25)

Method of angioplasty quality control	PG-PTA		C-PTA		*P*-value	
Number of limbs	54		56		–	
Mean age in years (±SD)	70 1 (±10 5)		71 7 (±10 1)		$P=0\ 420$	
Mean pre-angioplasty ABPI (±SD)	0 65 (±0 26)		0 66 (±0 23)		$P=0\ 781$	
Intermittent claudication/ rest pain or ulcer	$n=29$/ $n=25$		$n=22$/ $n=34$		$P=0\ 130$	
Location of angioplastied segment	Aorto-iliac $n=28$	Fem-pop $n=26$	Aorto-iliac $n=13$	Fem-pop $n=43$	$P=0\ 002$*	
Cumulative primary symptomatic success						
4 weeks	86%	77%	54%	63%	Aorto-iliac	Fem-pop
12 weeks	82%	73%	39%	51%	$P=0\ 005$*†	$P=0\ 13$
24 weeks	69%	67%	31%	51%		
Cumulative haemodynamic success						
4 weeks	71%	69%	54%	63%	Aorto-iliac	Fem-pop
12 weeks	68%	69%	31%	53%	$P=0\ 01$*†	$P=0\ 14$
24 weeks	62%	63%	21%	49%		
Complications/ amputations/ deaths	4/3/3		5/4/5		NA	

*χ^2 test, *† Log-Rank test

Conclusions: Our results suggest that pressure gradient guided angioplasty (PG-PTA) produces significantly better symptomatic and haemodynamic success rates in angioplasty of the aorto-iliac segment. However, this is not the case for femoro-popliteal segment angioplasty.

Vascular 018

Evaluation of claudication in patients after being discharged from an exercise programme

S. Dimitri, L. de Cossart, A. Roberts, K. Sykes, G. Cottorrell and P.R. Edwards

Countess of Chester Hospital, University College Chester

Aims: We reported earlier the results of a 3-month exercise program for claudicants. We are now reporting the results, 4 months after the patients were discharged from the programme.

Methods: Twenty-three claudicants were studied. Their maximum walking distance (MWD), heart rate (HR), oxygen consumption (VO_2), blood rheology and lipid profiles were measured.

Results: Twenty patients agreed to be retested while three declined. There were 15 men; mean age of 69.8 ± 7.03 years and five women; mean age 70.0 ± 3.5 years. 16 patients were ex-smokers, three non-smokers, and one patient continued to smoke. Significant parameters are shown in the table as mean (standard deviation).

	Pre-exercise	Post-exercise (3 month)	Post-discharge (4 month)	*P*-value
MWD meters	143.5* (18.33)	263.8 (40.02)	331.2* (49.76)	<0.001
Post-exercise HR	124.5* (5.19)	104.86 (3.55)	94.93* (5.05)	<0.001
Post-exercise ABPI	0.45* (5.25)	0.46 (5.47)	0.52* (4.63)	<0.02
Post-exercise lactate	2.6* (0.20)	2.2 (0.17)	1.4* (0.21)	<0.001
Cholesterol	5.7* (0.18)	5.3 (0.12)	4.9* (0.17)	<0.01
Plasma viscosity	1.8* (0.14)	1.7 (0.12)	1.6* (0.45)	<0.01

There was no significant change in resting HR, body mass index, resting ankle pressures, VO_2, and triglycerides.

Conclusions: The majority of patients continued to improve despite being discharged from the exercise programme. There was a 200% increase in walking distance despite no significant change in resting ABPI. Self-motivation, adaptation to walking and discontinuation of smoking might be the contributing factors.

SRS: Reperfusion Injury 1–9 — Wednesday 25 April 2001 16:00–17:30

Reperfusion Injury 001

The assessment of renal ischaemic injury during warm *ex vivo* perfusion

M.S. Metcalfe, W. Rohlke[1], R.N. Saunders, S.A. White, G.J. Murphy, R.M. Kimber, C. Mann and M.L. Nicholson

University Department of Surgery, Leicester General Hospital, UK and [1]Department of Biomaterials, University of Ulm, Germany

Aims: The use of non-heart-beating donors in renal transplantation is limited by concerns over organ viability, due to the warm ischaemic insult inevitably suffered prior to retrieval, the extent of which can be difficult to ascertain. Traditional organ preservation relies on hypothermia to reduce metabolic demand. However, this also prevents assessment of organ function. Therefore, the aim of this study was to subject ischaemically damaged kidneys to warm *ex vivo* perfusion, in order to assess how functional, physical and metabolic parameters correlate with the duration of warm ischaemia.

Methods: Twenty porcine kidneys were harvested from 35 to 45 kg Large White pigs, killed with an intracardiac overdose of phenobarbitone. The retrieval was performed through a midline laparotomy less than 10 min ($n=8$, group 1), 30 min ($n=6$, group 2) or 60 min ($n=6$, group 3) after cardiac arrest. After 2 h cold time, the kidneys were established on a pulsatile perfusion machine (Waters RM3), adapted to incorporate a heat and gas exchanger unit (Capiox SX10), with a systolic pressure set at 120 mmHg and temperature at 32°C. The perfusate used was a tissue culture fluid specifically tailored for the support of vascular endothelial cells, augmented with a perflourodecalin emulsion (12% w/v) to increase oxygen delivery, and albumin (60 g L^{-1}) to provide oncotic pressure. Perfusion parameters recorded after 1 h included the intrarenal vascular resistance, fractional sodium reabsorption, urine to perfusate ratios of creatinine, protein and glucose, and renal oxygen consumption. All results were compared using the Mann–Whitney U test.

Results: Vascular resistance was 0.24 (mL min^{-1} $mmHg^{-1}$ 100 g^{-1}) for group 1, 0.62** for group 2 and 0.78*** for group 3. Fractional sodium reabsorption was 0.26, 0.14* and 0.03,* respectively. Urine to perfusate ratios of creatinine were 5.35 in group 1, 6.12 in group 2, and 1.76 in group 3*. The ratios for protein were 0.07, 0.28*** and 0.92***, respectively, and for glucose 0.21, 0.62 and 0.92. Oxygen consumption (mL min^{-1} $100g^{-1}$) were 20.0 in group 1, 14.5* in group and 8.85** in group 3. (Values are median. *$P<0.05$, **$P<0.01$ and ***$P<0.001$, compared with group 1.)

Conclusion: Warm *ex vivo* perfusion of ischaemically damaged kidneys allows the measurement of functional and physical parameters the values of which reflect the duration of warm ischaemia. A transplant model is necessary to confirm the relationship of these parameters to organ viability.

Reperfusion Injury 002

Cardiac preservation is improved by the synergistic actions of magnesium and calcium

M.S. Attia, I. Ahmed, N. Ahmad, D.J. Potts† and J.P.A. Lodge

Department of Organ Transplantation, St. James' University Hospital and School of Biomedical Sciences†, University of Leeds, UK

Aims: We investigated the effects of adding magnesium (Mg^{2+}) and calcium (Ca^{2+} to phosphate buffered sucrose (PBS 140) solution to optimize cardiac preservation in an experimental model of 2-h ischaemia at room temperature.

Methods: Experiments were carried out in accordance with the Home Office guidelines. Three modifications of PBS140 were tested: PBS140+Mg (5 mmol L^{-1}), PBS140+Mg (5 mmol L^{-1})+Ca (0.25 mmol L^{-1}) and PBS 140+Mg (5 mmol L^{-1})+Ca (0.6 mmol L^{-1}). These concentrations of Mg and Ca were carefully chosen to avoid precipitation in the solution. Using an isolated rat heart model, hearts were subjected to 5 min of Langendorff followed by 15 min of working perfusion. Heart rate (HR), systolic pressure (SP), aortic flow (AF) coronary flow (CF) and cardiac output (CO) were measured every 5 min. This was followed by 10 min of cardioplegic infusion with the test solution at 22°C and storage at this temperature for 2 h. The hearts were then reperfused for 15 min in Langendorff, followed by 30 min in working mode. Cardiac functions were remeasured and expressed as percentage of their pre-ischaemic control values.

Results: Percentage recovery results are shown in the table.

	PBS140 ($n=8$)	PBS+5Mg ($n=6$)	PBS+5Mg+ 0.25 Ca ($n=6$)	PBS+5Mg+ 0.6 Ca ($n=7$)
No. hearts failed	2	0	0	0
HR recovery	88.9±2.7	87.3±2.2	91.5±2.4	92.2±3.5
SP recovery	81.8±1.3	82.8±4.6	84.2±2.4	90.0±2.2
AF recovery	49.0±4.1	59.8±6.8	53.0±3.3	82.8±1.5
CF recovery	65.2±8.4	74.9±5.2	70.3±3.4	81.6±4.6
CO recovery	54.9±5.6	63.3±6.6	57.8±3.4	68.8±4.6

Conclusions: Hearts preserved in PBS+Mg (5 mmol L^{-1})+Ca (0.6 mmol L^{-1}) achieved superior post-reperfusion cardiac function than with PBS 140 suggesting a role of these ions in optimising cardiac preservation.

Reperfusion Injury 003

Moderation of skeletal muscle reperfusion injury by Sialyl Lewis^x-soluble complement receptor type 1 (sLe^x-sCR1)

C. Kyriakides,[1] Y. Wang,[1] W.G. Austen Jr,[1] J. Favuzza,[1] L. Kobzik,[2] H. Marsh Jr,[3] F.D. Moore Jr,[1] H.B. Hechtman[1] and C.N. McCollum

Departments of [1]Surgery and [2]Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]AVANT Immunotherapeutics, Inc. Needham, MA, USA

Aims: The individual protective effects of the complement antagonist sCR1 and soluble sLe^x tetrasaccharide, which blocks neutrophil–endothelial selectin interaction, have been demonstrated in skeletal muscle reperfusion injury. This study examines the potentially enhanced anti-inflammatory effects of the sLe^x-decorated version of sCR1 *versus* non-sLe^x glycosylated sCR1.

Methods: Utilising a murine specific haemolytic assay, the *in vivo* complement inhibitory properties of sLe^x-sCR1 and sCR1 were investigated. Bilateral tourniquets were placed above the greater trochanter of anaesthetized C57BL/6 mice for 2 h, followed by 3 h of reperfusion. Extravasation of ^{125}I-albumin injected prior to reperfusion was used to assess hindlimb vascular permeability index (PI). Mice were treated with sLe^x-sCR1 or sCR1 before reperfusion and a dose response was obtained. Other groups of animals received sLe^x-sCR1 or sCR1 at various time points after reperfusion. Immunohistochemistry was performed. Animals were maintained in accordance with National Research Council guidelines.

Results: sLe^x-sCR1 and sCR1 had similar properties, providing 100% inhibition of classical and alternative complement pathways at a dose of 10 mg kg^{-1}, indicating that glycosylation of sCR1 does not interfere with its complement inhibitory properties. PI after subtraction of sham value (MEAN ± SE, $P<0.05$ by *t*-test with Bonferroni correction) in mice treated with 10 mg kg^{-1} sLe^x-sCR1 ($n=19$) was 0.91±0.08, a 62% reduction compared to the untreated group, PI 2.40±0.11 ($p<0.05$, $n=26$). Similarly, treatment with 10 mg kg^{-1} sCR1 demonstrated a 51% reduction in PI 1.18±0.07 ($p<0.05$, $n=18$). PI following treatment with 20 mg kg^{-1} sLe^x-sCR1 ($n=20$) was 0.73±0.06, a 70% reduction from the untreated group, and 20% less than the PI in 20 mg kg^{-1} sCR1 treated group, 1.19±0.08 ($P<0.05$, $n=19$), indicating that at least part of neutrophil mediated injury is complement independent. Reductions in PI observed in mice treated 0.5 h and 1 h after reperfusion but not before, with 20 mg kg^{-1} sLe^x-sCR1 of 0.90±0.07 (63%, $n=19$) and 1.24±0.09 (52%, $n=20$), were greater than the respective decreases in PI of 1.41±0.10 (41%, $n=18$) and 1.61±0.07 (32%, $n=20$) seen in 20 mg kg^{-1} sCR1-treated groups ($P<0.05$). No significant reduction in permeability was observed in mice treated 2 h after reperfusion with either sLe^x-sCR1 or sCR1. Immunohistochemistry obtained at 0.5 h and 1 h after reperfusion, stained for sCR1 only on the vascular endothelium of sLe^x-sCR1 treated mice, indicating an ability to localize at the site of endothelial selectin activation.

Conclusions: sLe^x-sCR1 attenuates injury more effectively than sCR1 by its localising ability on activated endothelium, leading to both antagonism of complement activation and neutrophil adhesion. Significantly, delayed complement and neutrophil antagonism moderates injury.

Reperfusion Injury 004

Pravastatin preserves endothelial dependent vasomotor function in an experimental model of diabetes mellitus

D. Moneley,[1] C. Gang,[1] E. Kay,[2] C. Thompson,[3] C.J. Kelly[1] and D.J. Bouchier-Hayes[1]

Department of Surgery,[1] *Pathology,*[2] *and Endocrinology,*[3] *RCSI, Dublin, Ireland*

Aims: The aim of this study was to investigate the effect of pravastatin on ischaemia reperfusion (IR)-induced vasomotor dysfunction in the microvasculature of the diabetic.

Methods: Sprague–Dawley rats ($n = 18$) were randomized into 3 groups: (a) control; (b) diabetic; (c) diabetic treated with Pravastatin. A mesenteric arteriole was examined pre and post I-R using intra-vital microscopy. Endothelial dependent and independent vasodilatation, measured by response to acetylcholine (Ach) and sodium nitroprusside (SNP), respectively, was measured in mesenteric arterioles pre-constricted with noradrenaline. The arteriolar constriction: dilatation ratio (C:DR) was then calculated.

Results: Expressed as mean ± SEM following 60 min of reperfusion.

Group	Ach (C:DR)	SNP(C:DR)
Control	1.6 ± 0.085	1.98 ± 0.01
Diabetic	1.16 ± 0.049$	1.91 ± 0.03
Diabetic/Pravastatin	1.78 ± 0.04*	1.96 ± 0.07

*$P < 0.01$ versus diabetic. $$P < 0.01$ versus control ANOVA, Tukey–Kramer *post hoc* test.

This data demonstrates a restoration of endothelial dependent vasomotor function in the treated diabetic group compared with untreated.

Conclusions: We have shown that pravastatin in an experimental model of diabetes mellitus preserves endothelial function following I-R, and this effect is independent of its cholesterol lowering effects.

Reperfusion Injury 005

Does near infrared spectroscopy detect normovolaemic haemodilution?

F. Torella, S.L. Haynes, D. O'Brien and C.N. McCollum

Academic Surgery Unit, South Manchester University Hospital, Manchester, UK

Aims: During haemorrhage, transfusion is often given on vague clinical grounds. As blood loss in experimental models relates to increased tissue oxygen extraction on near infrared spectroscopy (NIRS), we evaluated NIRS as a possible transfusion trigger in a model of compensated haemorrhage in man.

Methods: Regional haemoglobin saturation in the brain ($\mathrm{CsO_2}$ – left frontal area) and left calf ($\mathrm{PsO_2}$) was measured by INVOS 4100 oximeter (Somanetics) during acute normovolaemic haemodilution (ANH) to a haemoglobin of 11 g dL^{-1} in 15 patients prior to surgery. Patients also underwent continuous monitoring of blood pressure (via an arterial line) arterial saturation and end tidal carbon dioxide concentration. Differences were compared with the paired t-test and within subjects correlation measured by analysis of co-variance.

Results: During ANH, $\mathrm{CsO_2}$ decreased by a mean (95%CI) of 8 (3.4–11.9)% ($P = 0.002$) and $\mathrm{PsO_2}$ decreased by a mean (95%CI) of 6 (2.4–10.3)% ($P = 0.004$). There was a good correlation between progressive blood loss, $\mathrm{CsO_2}$ ($r = -0.56$; $P < 0.001$) and $\mathrm{PsO_2}$ ($r = -0.72$; $P < 0.001$). When adjusted for mean arterial pressure, arterial saturation and end tidal carbon dioxide tension, the change seen in correlation coefficients for $\mathrm{CsO_2}$ ($r = -0.58$; $P < 0.001$) and $\mathrm{PsO_2}$ ($r = -0.66$; $P < 0.001$) was small.

Conclusion: Regional haemoglobin saturation correlates closely to blood loss and the influence of blood pressure, arterial saturation and pH is small. A transfusion trigger may be developed if these results are confirmed by clinical studies.

Reperfusion Injury 006

Hepatic hypoperfusion after intestinal ischaemia–reperfusion injury

S.B. Williams,[1,2] S.R. Williams[3] and A. Pierro[2]

[1]*RCS Unit of Biophysics and* [2]*Department of Paediatric Surgery, Institute of Child Health, University College London, London, UK, and* [3]*Imaging Science and Biomedical Engineering, University of Manchester, Manchester, UK*

Aims: Intestinal ischaemia–reperfusion injury (IR) is a common surgical emergency in both adult and paediatric surgical practice, and we have shown that it is associated with hepatic energy failure upon reperfusion. We studied hepatic inflow during intestinal IR to evaluate any changes that may affect liver energy metabolism.

Methods: Two groups of adult male rats were studied under Home Office licence. Both groups were anaesthetized, the superior mesenteric artery (SMA) exposed, and ultrasonic transit-time flow-probes sited on the both the hepatic artery (HA) and portal vein (PV). Continuous blood flow recordings were made from the HA and PV simultaneously for 20 min. HA and PV flow were added to give total hepatic inflow. The intestinal IR group had the SMA occluded for 90 min, then de-occluded, and the mid-gut reperfused for a further 60 min. The sham operation group had no SMA occlusion.

Results: The sham operation group ($n = 3$) did not show a consistent change in total hepatic inflow over the experiment, maintaining inflows of between 115% and 86% of initial values at 170 min. The intestinal IR group ($n = 4$) showed an instantaneous drop in total hepatic inflow on SMA occlusion, which was maintained throughout intestinal ischaemia (56%–76% of initial inflow). On reperfusion of the mid-gut, hepatic inflow showed an immediate increase, to approach pre-SMA occlusion levels, followed by a decline over the 60 min reperfusion period. At the end of the experiment inflow had fallen to levels of between 48% and 31% of initial inflow, i.e. less than inflow during intestinal ischaemia.

Conclusions: Intestinal IR causes a dramatic fall in hepatic inflow, which may contribute significantly to the changes seen in liver energy metabolism already noted in this model.

Reperfusion Injury 007

Pravastatin restores ischaemia–reperfusion induced diapragmatic dysfunction

D. Moneley, C. Condron, R. McLaughlin, C.J. Kelly and D.J. Bouchier-Hayes

Department of Surgery, Royal College of Surgeons in Ireland, Dublin, Ireland

Aims: Respiratory dysfunction was the greatest predictor of morbididty in the recent UK small aneurysm trial. Our aim was to investigate the therapeutic role of pravastatin on ischaemia–reperfusion (IR)-induced diaphragmatic dysfunction.

Methods: Male Sprague–Dawley rats ($n = 18$), were randomized into 3 groups: (a) control; (b) IR; and (c) IR treated with pravastatin for 5 days pre-operatively. IR was achieved by placing an infra-renal aortic clamp for 30 min followed by 2 h of reperfusion. Diaphragm muscle contractile function was assessed using electrical field stimulation in a tissue bath.

Results: Expressed as peak tension and fatigability.

Group	Twitch (sEM) (g)	Tetanus (SEM) (g)	Fatigability (SEM) (s)
Control	242.01 (38.45)	605.52 (77.63)	34.31 (4.6)
IR	108.55 (7.15)$	228.12 (14.38)$	25.5 (6.6)
IR + rhGH	220.14 (30.71)*	540.39 (45.69)*	30.1 (2.07)

*$P < 0.01$ *versus* IR, $ $P < 0.05$ *versus* Control. Kruskal-Wallis ANOVA.

Conclusions: We conclude that pravastatin significantly attenuates ischaemia–reperfusion induced diaphragmatic dysfunction and this observed effect may benefit patients undergoing elective vascular reconstruction.

Reperfusion Injury 008

Pravastatin attenuates ischaemia–reperfusion induced renal injury in an experimental animal model

M. Joyce, C.J. Kelly, G. Chen, E. Kay, G. McGreal, D.C. Winter, C. Condron, A. Leahy and D.I. Bouchier-Hayes

Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland

Aims: Renal dysfunction due to ischaemia–reperfusion (I-R) may result from suprarenal aortic cross-clamping and from renal transplantation. Statins *in vitro* have been cytoprotective of hypoxia by upregulation of constitutive endothelial nitric oxide synthase (ecNOS). We hypothesized that pravastatin would attenuate I-R induced renal injury.

Methods: Male Sprague–Dawley rats ($n = 21$) were randomized into three equal groups. Control (uninephrectomy only), I-R group and an I-R group pre-treated with pravastatin (4 mg kg^{-1} day^{-1} over 5 days). I-R injury was induced by clamping the renal vascular pedicle for 30 min followed by reperfusion for 2 h. Western blotting was used to determine the expression of ecNOS.

Results:

	Control	I-R group	Pravastatin
Urine production (mL)	1.23 (0.27)	0.22 (0.1)*	1.25 (0.4)
GFR (mL h^{-1})	14.14 (0.9)	1.31 (0.5)*	8.6 (0.97)
TUPL (g L^{-1})	1.67 (0.12)	7.21 (1.3)*	3.76 (0.7)
Densitometric values for ecNOS relative to control	100%	94%	300%

Data are expressed as mean (SEM). Analysis with ANOVA, *post hoc* Scheffé test. *$P<0.05$ *versus* control and pravastatin groups

Conclusions: Pravastatin attenuates IR-induced renal injury by a mechanism of action involving up-regulation of constitutive endothelial nitric oxide synthase

Reperfusion Injury 009

Vitamin C attenuates ischaemia–reperfusion induced acute muscle injury

S R Kearns,[1] D Moneley,[2] P Murray,[1] C. Kelly[2] and D J. Bouchier-Hayes[2]

[1]*Departments of Orthopaedics Cappagh Hospital and* [2]*Department of Surgery RCSI, Beaumont Hospital, Dublin, Ireland*

Aims: Following ischaemia–reperfusion tissues undergo a neutrophil-mediated oxidant injury. Our aim was to evaluate vitamin C supplementation in the prevention of I-R induced acute muscle injury.

Methods: Sprague–Dawley rats ($n=6$ per group) were randomized into control, I-R and I-R pretreated with vitamin C (3.3g over 5 days). Cremasteric muscle was isolated on its neurovascular pedicle and I-R injury was induced by clamping the pedicle for 3 h, the tissue was subsequently reperfused for 60 min. Muscle function was assessed by electrical field stimulation: peak twitch, maximum tetanus values were recorded. Tissue neutrophil infiltration was assessed by tissue myeloperoxidase activity and tissue oedema by wet-to-dry ratio

Results: Ischaemia–reperfusion resulted in a significant decrease in muscle twitch and tetanic contraction and an increase in neutrophil infiltration and tissue oedema. Pre-treatment with vitamin C-attenuated I-R injury as assessed by all parameters

	Peak twitch	Maximum tetanus	MPO	Wet dry ratio
Control	160.7±23.1	451.6±47.7	5.4±0.44	0.93±0.09
I-R	47.0±5.9 *	239.4±18.7*	8.2±0.59 *	1.28±0.06*
I-R & Vitamin C	74.7±4.6**	394.7±28.7**	5.6±0.41**	1.01±0.04**

Mean ± SEM, * $P<0.01$ *versus* Control, ** $P<0.05$ *versus* I-R (ANOVA). I-R, ischaemia–reperfusion, MPO, myeloperoxidase

Conclusions: These data suggest that oral vitamin C attenuates I-R induced acute muscle injury, possibly by reducing neutrophil mediated tissue injury

ASGBI: Superficial Abscesses 1–2 Wednesday 25 April 2001 09:30–10:00

Superficial Abscesses 001

The evolution of a day-case abscess service

I.M. Loftus, L.P. Cheah, D.F.L. Watkin and D.P. Fossard
The Leicester Royal Infirmary, Leicester LE1 5WW

Introduction: The Royal College of Surgeons in its Guidelines for Day Case Surgery (1992) states that 'day surgery is now considered the best option for 50 per cent of all patients undergoing elective surgical procedures'. However, this concept has not been extended to more urgent procedures. In 1994 we established a day-case service for patients with superficial abscesses.
Aims: The aim of this study was to re-audit the service to assess its structure and effectiveness and the appropriateness and pattern of referrals.
Methods: We performed a prospective audit of the treatment of 100 consecutive patients with abscesses treated as day cases between October 1999 and January 2000, and compared this to the first 100 patients treated on the service in 1994.
Results: There has been a dramatic increase in the use of the service with 100 patients treated in 107 days compared to 8 months in the initial audit, largely due to increased GP referrals. In the recent audit, 70 per cent were treated within 3 h of admission compared to 57 per cent in the first period, with smaller abscesses being referred and drained under local anaesthetic.
Conclusions: The day-case abscess service has achieved its initial aim to reduce inpatient waiting time for surgical treatment. However, the accessibility of the service has led to an increase in referrals and perhaps reluctance on the part of GPs and Accident and Emergency services to treat abscesses themselves.

Superficial Abscesses 002

Prospective randomized controlled trial of the effectiveness of emergency day surgery against standard in-patient treatment

P.J. Conaghan, E. Figueira and C.L. Ingham Clark
Department of Surgery, Whittington Hospital, Highgate Hill, London

Aims: To assess effectiveness of emergency day surgery against standard in-patient care.
Methods: Emergency adult referrals for minor and intermediate general surgical conditions were assessed. Those fitting day-case criteria and requiring surgery were randomized to be treated as day-case emergencies or receive standard inpatient care. Those in the day-case arm were booked onto gaps in day case or inpatient elective lists for surgery within 48 h. Patients in the inpatient arm were admitted and added to the emergency list for treatment according to priority. Delay to treatment and bed-night usage were measured for each patient and the two groups compared using a Mann–Whitney analysis. Patients were reviewed at 1 month following surgery when pain scores, involvement of primary care services and patient satisfaction were assessed. It is estimated that 100 patients will be required to ensure reasonable power in all outcome measures.
Results: Seventy patients (35 day-case) have entered the study in the 6 months to May 2000. A further 16 patients who refused randomization have been followed in an unrandomized group according to preference. There were no readmissions within 30 days and no significant complications in either group. Median bed-night occupancy was 0 days (range 0–2) in the day case group and 2 (range 1–2) in the inpatient group ($P<0.001$). There was no significant difference in delay from hospital attendance to definitive treatment between the groups. In the day-case group, 67 per cent were treated in the day surgery unit itself with the remainder being treated as day cases on inpatient wards. Those treated in the day surgery unit had a significant reduction in bed-night occupancy compared to those treated as day cases on inpatient wards – a median bed night stay of 0 days (range 0–1) *versus* 1 day (range 0–2) ($P=0.002$). Post-operative follow-up to date shows high level of patient satisfaction irrespective of group and no difference between the groups in either pain scores or in use of primary care services.
Conclusions: Although the study is still in progress, it appears that treating minor and intermediate surgical emergencies as day cases reduces the time spent in hospital without prolonging time to treatment or reducing the standard of care. Data from the study also suggest that the philosophy of an integrated day surgery unit is important for emergency day surgery as has been shown for elective day case surgery. These results have considerable financial implications for hospitals.

ASGBI: Emergency Service 1–3

Wednesday 25 April 2001 16:10–16:40

Emergency Service 001

The changing profile of emergency surgical admissions: a study of the years 1974–1998

W.B Campbell, E J K Lee, K van de Sype, J Gooding and M J Cooper
Department of Surgery, Royal Devon and Exeter Hospital, Exeter EX2 5DW

Aims: The aim of this study was to document changes in the numbers of emergency admissions in general surgery and urology, in the proportions of different diagnoses, the need for operative intervention, the length of hospital stay and mortality. This was done by retrospective analysis of computerized data for every fourth year from 1974 to 1998 inclusive, a total of seven separate calendar years. The setting was a district general hospital with a relatively stable population, and a catchment area which increased from 281 000 to 335 485 during the 25 years study interval
Methods: A total of 19 931 patients were admitted during the seven years studied, with a steady increase from 2137 in 1974 to 3578 in 1994, and a small decrease to 3377 in 1998 The mean age of patients admitted increased from 47 9 years to 52 6 years. The proportion having operations during their emergency admission increased from 48.2 per cent in 1974 to 58 8 per cent in 1998, but despite this the mean length of stay decreased from 9 5 days to 5 3 days Hospital mortality fell from 6 6 per cent to 3 7 per cent
Results: Diagnoses that became significantly more frequent were ruptured abdominal aortic aneurysms, gallstones, constipation, cutaneous abscess, diverticular disease, gastroenteritis, non-specific abdominal pain, pilonidal sinus, and all urinary diagnoses Diagnoses which became significantly less common were appendicitis and non-malignant intestinal obstruction
Conclusions: These observations confirm an impression of increasing workload and shorter hospital stay. Although there have been large increases in admission of conditions such as non-specific abdominal pain and constipation, which do not require surgery, the proportion of patients having operations during their emergency admission has increased.

Emergency Service 002

'Consultant of the week' impact on emergency surgery and surgical training

C A Harris, M J S Wilkinson and D G. Ostick
Royal Bolton Hospital, Minerva Road, Farnworth, Bolton

Introduction The Royal Bolton Hospital is a district general hospital with a catchment area of approximately 275 000 for elective admissions, but nearer 400 000 for emergency admissions Eight consultant general surgeons with subspecialty interests cover the emergency surgical referrals From 1st Jan 2000 a 'consultant of the week' system has been introduced One week in eight the consultants normal duties are cancelled, and for this week they cover directly the middle grade staff member that is on call from the hours of 8am to 5 pm The middle grade staff member also has no clinical duties for that week After 5 pm the patients are handed over to the evening on call team as per the normal rota Prior to this arrangement the consultant on call had no relief from clinical duties between the hours of 8am to 5 pm We have 24 hour access to an emergency theatre shared with other surgical specialities except obstetrics
Aims: To identify what differences this change has made in the provision of emergency services at this hospital
Methods: An audit comparing the first 6 months of 1999 to the first 6 months of 2000, using theatre databases
Results: In the first six months of 1999 there were 572 emergency procedures performed and in 2000 there were 615 procedures performed The consultant was the principal operator in 132 (23 per cent) of these cases in 1999 and 209 (34 per cent) in 2000 314 cases were performed between 8am and 5 pm in 1999 and 348 in 2000, of these cases, the consultant was the principal operator in 87 (28 per cent) in 1999 and 151 (43 per cent) in 2000 In the 8am to 5 pm time period the consultant was assisting in 10 cases in 1999 and 22 cases in 2000. The consultant's involvement in cases outside this time period and number of cases performed was remarkably similar in 1999 and 2000
Conclusions: Switching to 'consultant of the week' has led to greater consultant participation in the emergency cases between 8am and 5 pm and lead to an increase in junior surgeon supervision in the same time period It has not altered the consultant's workload out of hours

Emergency Service 003

Emergency admissions: who managed whom, when and who did they tell? Scottish audit of surgical mortality (SASM)

J Nagy, G D Griffiths, J Bannister, A M. Thomson and P A Stonebridge
Department of Surgery, Ninewells Hospital and Medical School, Dundee

Aims: To review consultant surgeon and consultant anaesthetist input by time of operation for patients admitted as emergencies and dying under surgical care
Methods: SASM 1998 data of deaths under surgical care were used to identify ASA grade, time into anaesthetic room, grade of surgeon, grade of anaesthetist and the most senior clinician with whom the case was discussed
Results: Data were examined from 1195 cases admitted as emergencies in Scotland who subsequently underwent surgery and died 74 per cent were operated between 08.00 and 17·59 and were mainly of ASA grade 3/4 26 per cent of cases were operated between 18 00 and 07.59 and the majority were ASA 4/5. Analysis of consultant involvement in both ASA 4 and patients at high risk was performed. Consultant involvement in ASA 4 patients who subsequently die by time of operation

Consultant	Surgeon	Anaesthetist	Surgeon	Anaesthetist
Absent	4%	14%	5%	17%
Discussed	33%	8%	31%	15%
Present	63%	78%	64%	68%
Time	08 00	17 59	13 00	17 59
Absent	9%	8%	11%	20%
Discussed	15%	29%	20%	29%
Present	76%	63%	69%	51%
Time	18 00	21 59	22 00	07 59

Conclusions: ASA grade 4 patients were chosen for this analysis as it could be argued they stand to benefit most from consultant care compared to ASA grade 5 patients in whom the comorbidity and severity of surgical illness makes survival unlikely or ASA grade 1, 2 and 3 patients who would be expected to do well Consultant surgical and anaesthetic awareness (either by their presence in theatre or by having discussed the case) was generally high (never less than 80 per cent) and is to be commended. Nevertheless, examining the degree of consultant involvement by time of day provides insight into how the care of these patients may be further improved During normal working hours, consultant surgeons were aware of 95 per cent of these cases, but were only present for 64 per cent. Consultant anaesthetist awareness of these cases was less than that of the surgeons, but they were more likely to be in theatre if they did know about them These figures suggest that trainee surgeons are more likely to discuss high-risk patients with their consultants than are trainee anaesthetists This is likely to be a feature of surgical team working fostering communication to a greater extent than do anaesthetic working patterns The greater consultant anaesthetic availability during the day may relate to their not having any other commitments when on call Consideration should be given to the cancellation of a surgical consultant's elective work when receiving emergencies. Out of hours, the degree of anaesthetic consultant awareness of these cases was similar to that within normal working hours Surgical consultant awareness was somewhat less, however, suggesting a reluctance by trainees to telephone their consultants at home Consultant surgical presence was similar to that during normal working hours while consultant anaesthetic presence fell, particularly overnight If it is accepted that the patients studied here stand to benefit from direct consultant involvement, then there is no reason why consultant presence out of hours should not be greater than it is during normal working hours This would have considerable implications with respect to hours worked and would require consultant expansion or amalgamation of smaller units Two further points are worthy of mention Firstly, with the changes in traditional surgical team-working, the apparently good daytime communication demonstrated in this study may be worsened and steps should be taken to ensure this does not happen Secondly, there has to be awareness among trainees and consultants that the Calman system has delayed the acquisition of experience We should not fall into the trap of trainees having insufficient experience to realise they are out of their depth While consultant involvement in this study was quite good, it should be improved if we are to be able to demonstrate optimal patient care This will require changes in working patterns that will have resource implications The failure to respond will be detected by, and have great impact on, clinical governance

ASGBI: British Obesity Surgery Society — Wednesday 25 April 2001 17:20

BOSS 001

Twelve-year experience with gastric bypass and vertical banded gastroplasty for morbid obesity

C.J. O'Boyle, D. Walters, D.I. Watson and P.A. Game

Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia

Aims: The diversity of corrective surgical procedures for morbid obesity is a testament to the absence of any one ideal intervention. We compared our 12 years' experience with the two most common operations: vertical banded gastroplasty (VBG) and gastric bypass (GBYP), with particular regard to short and long-term complications, failures and efficacy of weight loss.

Methods: Between January 1988 and January 2000 all obesity surgery data was prospectively entered into a dedicated database (Fatstat, Microsoft Access). This data was retrieved for the purposes of the study.

Results: Two hundred and four patients (62 per cent) underwent GBYP of which 127 (62 per cent) had had no previous intervention. One hundred and five patients underwent VBG of which 88 (84 per cent) had had no previous intervention. Eighty two percent were female. The mean ages were similar (39 (5) *versus* 37 (4), $P=\mathrm{ns}$). Preoperative mean (SEM) excess weight were slightly higher for VBG patients (103 (34) *versus* 116 (41), $P=(\mathrm{ns})$. Major complications occurred less frequently in GBYP patients (10 (8 per cent) *versus* 28 (32 per cent), $P<0.001$). At 1 year following surgery, the mean percent excess weight loss was greater for GBYP (78 (15) *versus* 60 (28), $P<0.05$). This weight loss was sustained at 4 years follow-up (76 (15). However, mean excess weight loss had reduced for the VBG patients (45 (51), $P<0.05$). Revisional surgery was required in less GBYP patients (four (3 per cent) *versus* 23 (26 per cent), $P<0.001$).

Conclusions: Open gastric bypass surgery for morbid obesity is associated with fewer major complications, fewer failures and a greater and more durable excess weight loss.

ASGBI: Moynihan 1–6

Thursday 26 April 2001 09:15–10:45

Moynihan 001

A human model of duodeno-gastro-oesophageal reflux in the development of Barrett's metaplasia

S M Dresner, J Wayman, M K Bennett, N Hayes and S M Griffin

Northern Oesophago-Gastric Cancer Unit, Ward 36 Office, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Aims: Although Barrett's oesophagus (BO) is believed to result from chronic reflux of foregut contents, its exact aetiology and pathogenesis remain uncertain. Following oesophagectomy and intrathoracic oesophago-gastrostomy patients experience profound duodeno-gastro-oesophageal reflux (DGOR) into the oesophageal stump and provide a potential human model in which to study the early events in the development of Barrett's metaplasia.
Methods: One hundred patients (median age 58 years, range 28–77, M:F ratio of 4:1) comprising postoesophagectomy ($n = 40$), complicated BO ($n = 15$), uncomplicated BO ($n = 15$), reflux oesophagitis ($n = 15$) and controls without erosive changes ($n = 15$) were studied using endoscopy, systematic biopsy, oesophageal manometry and 24-h ambulatory pH and biliary monitoring. Biopsy material was analysed immunohistochemically to calculate a proliferation index using the Ki-67 nuclear labelling technique.
Results: Original indications for resection in patients studied after oesophagectomy were adenocarcinoma ($n = 26$) and squamous carcinoma ($n = 14$). Surgical technique was identical in all cases with curative intent and clear upper resection margins showing normal squamous epithelium. At a median of 38 months (13–178) after surgery a median of two (1–7) endoscopies have revealed normal appearances in seven cases, grade 1–3 squamous oesophagitis in 14 cases and columnar epithelium in the oesophageal stump in 19 cases. Biopsy material from columnar regeneration revealed cardiac type epithelium in 10 cases and goblet cell metaplasia in nine cases at a median of 56 months (13–178) from surgery. Seven patients followed serially demonstrated progression from squamous to cardiac mucosa and from cardiac epithelium to intestinal metaplasia (IM). Compared to patients with intact squamous mucosa, patients with neo-Barrett's segments had significantly higher 24-h acid and bile exposure ($P = 0.01$). DGOR in this latter group was similar to that in patients with established BO with complications which in turn was significantly higher than in those with uncomplicated BO, reflux oesophagitis and no erosive changes ($P = 0.004$). Across this spectrum of reflux disease a significantly higher incidence of motility disturbance ($P = 0.03$) and decreased lower oesophageal sphincter pressure ($P = 0.02$) was also noted. In both squamous and Barrett's epithelium, proliferative activity correlated strongly with increasing acid and biliary reflux ($P < 0.05$).
Conclusions: BO develops from squamous epithelium upon a background of severe DGOR via a sequence of cardiac epithelium and subsequent IM. The correlation between increasing DGOR, epithelial proliferation and a worsening clinical spectrum of reflux disease suggests synergism between gastric and duodenal contents in the production of oesophageal mucosal injury.

Moynihan 002

How does carotid surgery influence cognitive function?

S J Fearn, K Wesnes,[1] G Riding, S Hutchinson, G Hill-Wilson and C N McCollum

South Manchester University Hospital Trust, and [1]Cognitive Drug Research, Reading, UK

Aims: Surgeons often report patients seem brighter after carotid endarterectomy (CEA) but this has never been proven. Assessing cognitive function as an overall score ignores the possibility that there may be selective effects on different aspects such as attention, information processing and memory.
Methods: Patients ($n = 159$, median age 68 years) were investigated during CEA by ipsilateral transcranial Doppler of middle cerebral artery flow velocity (MCA flow) and embolization. Regional oxygen saturation (CsO_2) was measured by near infrared spectroscopy. Cerebrovascular reactivity (CVR) to inhaled carbon monoxide was measured before surgery in 92 patients. Cognitive function was measured using a standardized battery of tests produced and validated by Cognitive Drug Research (Reading, UK) before surgery and 1 and 8 weeks later, and compared to controls undergoing urological procedures ($n = 19$, median age 74 years).
Results: There was a deterioration in attention compared to controls 1 week following CEA ($P = 0.003$ Mann–Whitney *U*-test). This deterioration correlated with the number of emboli ($r = 0.2$, $P = 0.03$ Spearman) and low MCA flow on declamping ($r = 0.3$ $P = 0.002$ Spearman). Despite this initial deterioration, attention reaction times improved significantly at 8 weeks compared to preoperative values (median 1247 s to 1193 s $P < 0.001$ Wilcoxon). This improvement was greatest in patients with severely impaired CVR at <34 per cent ($P = 0.02$). High MCA flows generally correlated with improvements in attention as did CsO_2 after cross-clamping and on declamping ($r = 0.2$, $P = 0.04$, respectively).
Conclusion: CEA improves attention in patients with impaired CVR.

Moynihan 003

Dynamic contrast MRI (DCMRI) assessment of tumour permeability in locally advanced rectal cancer: a prognostic indicator for response to chemoradiotherapy

M L George,[1,4] A.S K Dzik-Jurasz,[2] G. Brown,[3] A R Padhani,[2] J Husband,[3] M O. Leach,[2] I J Rowland,[2] M E Hill,[5] D C Cunningham,[5] D. Tait,[5] S A Eccles[4] and R I Swift[1]

[1]Department of Surgery, Mayday University Hospital, Thornton Heath, Surrey,[2]CRC Clinical Magnetic Resonance Research Group and [3]Academic Department of Medical Imaging, Royal Marsden NHS Trust, Downs Road, Sutton and [4]Section of Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey and [5]Department of Medicine, Royal Marsden NHS Trust

Aims: The assessment of angiogenesis by microvessel density, immunostaining and RT-PCR is normally performed on surgically resected specimens. However, noninvasive methods, such as MRI and serum/plasma, are able to indirectly assess angiogenesis both preoperatively and during treatment. This study examines whether tumour vascular permeability, assessed by DCMRI and serum VEGF, may be a useful predictive marker in locally advanced rectal cancers undergoing chemoradiotherapy.
Methods: 31 patients with locally advanced adenocarcinoma of the rectum (T3/T4) were assessed. All examinations were carried out on a 1.5 T magnet using a pelvic phase array coil. A 10 mm slice through the main bulk of the tumour was defined after imaging the full extent of the tumour, and tumour permeability measured using Tofts model. Serum and plasma VEGF samples were taken from the patients just prior to entering the magnet and measured by ELISA. 16 patients underwent chemoradiotherapy prior to surgical resection. Subsequent MRI scans were used to assess the response of the tumour to chemoradiotherapy according to WHO criteria.
Results: At presentation, there was a significant correlation ($r = 0.48$, $P = 0.0099$) between DCMRI tumour permeability and serum VEGF. Seven patients responded (8 SD and 1 PD). There was a significant difference in tumour permeability at presentation between responders and non-responders, with responsive tumours being more permeable (−0.41 and −0.77, $P = 0.0012$ respectively). There was no significant difference in tumour permeability in either group after 12 weeks chemoradiotherapy compared with the initial tumour ($P = 0.012$).
Conclusion: Rectal cancers that are highly angiogenic, as assessed by DCMRI tumour permeability, are more sensitive to chemoradiotherapy than tumours with lower permeability. This may allow for improvement in the selection of rectal cancer patients planned to receive preoperative adjuvant therapy.

Moynihan 004

Avoidance of excess saline administration postoperatively allows earlier recovery of gastrointestinal function, reduces complications and shortens postoperative stay: a prospective, randomized controlled study

D N. Lobo, K A Bostock, K R. Neal, A C Perkins, B J Rowlands and S P Allison

University Hospital, Queen's Medical Centre, Nottingham

Aims: To determine whether avoidance of postoperative salt and water overload results in accelerated recovery of gastrointestinal function and improved outcome in patients undergoing elective colonic resections.
Methods: This randomized controlled study was conducted on 20 patients with no premorbid conditions other than colonic cancer, randomized into normal postoperative management (NPM) and salt and water restriction (SWR) groups. The NPM group ($n = 10$) received postoperative fluids according to current hospital practice (i.e. at least 3 L water and 150 mmol sodium/day) while the SWR group ($n = 10$) received no more than 2 L water and 75 mmol sodium day^{-1}. The primary end point was solid and liquid phase gastric emptying time as measured by dual isotope radionuclide scintigraphy on the fourth postoperative day. Secondary end points included

time to passage of flatus, first bowel movement, and postoperative hospital stay. Postoperative complications were also noted. Statistical significance was calculated using the Mann–Whitney *U*-test.

Results:

End point	NPM group ($n = 10$)	SWR group ($n = 10$)	*P*-value
T_{50} Solid phase gastric emptying time [Median (IQR) min]	175 (105–201)	73 (54–149)	0.028
T_{50} Liquid phase gastric emptying time [Median (IQR) min]	110 (85–171)	74 (33–88)	0.017
Time to first passage of flatus [Median (IQR) days]	4.0 (4.0–5.0)	3.0 (2.0–3.0)	0.001
Time to first bowel movement [Median (IQR) days]	6.5 (5.8–8.0)	4.0 (3.0–4.0)	0.001
Postoperative hospital stay [Median (IQR) days]	9.0 (7.8–14.3)	6.0 (5.0–7.0)	0.001

Seven patients in the NPM group and none in the SWR group developed peripheral oedema. There were no complications in the SWR group while two patients in the NPM group had infective complications and three had prolonged postoperative confusion. There were no deaths or readmissions within 30 days of the operation in the SWR group. One patient in the NPM group was readmitted and died of lymphangitis carcinomatosi within 30 days.

Conclusions: Avoidance of excess administration of salt and water after elective colonic resections allows earlier recovery of gastrointestinal function, reduces complications and shortens hospital stay.

Moynihan 005

Rapamycin does not improve renal function or reduce profibrotic gene expression in chronic allograft nephropathy

R.N. Saunders, M.S. Metcalfe, G.J. Murphy, G.R. Bicknell, S.A. White and M.L. Nicholson

University Department of Surgery, Leicester General Hospital, Leicester, UK

Introduction: Chronic allograft nephropathy (CAN) is the most common cause of late renal allograft failure. Overexposure to cyclosporin (CyA) causes chronic nephrotoxicity, an important aetiological factor for CAN and thus CyA does reduction has been advocated. Experimental evidence suggests that rapamycin (Rapa), a new immunosuppressant, may retard the development and progression of CAN. The aim of this study was to determine the functional and molecular impact of the addition of Rapa after CyA dose reduction compared to CyA dose reduction alone.

Methods: Thirty-one renal transplant recipients with CAN were prospectively randomized to receive either a 40 per cent dose reduction in CyA (control, $n = 15$), or a 40 per cent dose reduction in CyA with the addition of Rapa 2 mg day^{-1} ($n = 16$). Patients had a renal allograft biopsy on recruitment and were followed up clinically for 6 months after which a further biopsy was performed. Glomeruli were plucked from the surface of each biopsy core and total mRNA extracted using oligo-DT dynabeads. Complementary DNA was synthesized by reverse transcription and the polymerase chain reaction was used to amplify specific mRNA species. These were quantified using an ELISA technique, levels compared to the expression of the housekeeping gene GAPDH and expressed as arbitrary units.

Results: Both groups were well matched in terms of patient characteristics and mean (SD) CyA trough levels after dose reduction (Rapa 68 ± 21 *versus* control 56 ± 19 n /mL^{-1}). Control patients had a mean (±SD) Cr-51 labelled radioisotope GFR of 29.5 ± 10.4 mL min^{-1} at entry and 27.0 ± 8.0 mL min^{-1} ($P = 0.25$) after 6 months although the rate of decline of estimated GFR over the study compared to the pretrial 6 months showed a marginal improvement (c0.24 ± 0.21 pre *versus* −0.04 ± 0.27 mL min^{-1} week^{-1} post, $P = 0.07$). However Rapa patients had a significant fall in radioisotope GFR from 31.6 ± 8.9 to 27.3 ± 8.6 mL min^{-1} ($P = 0.003$) and the rate of decline in GFR remained unchanged (−0.03 ± 0.13 pre *versus* −0.16 ± 0.27 mL min^{-1} week^{-1} post). CyA dose reduction alone caused a reduction in mean (SD) TGFβ expression (0.48 (0.33) pre *versus* 0.25 (0.14) post, $P < 0.05$) and an increase in iNOS expression (0.12 (0.06) pre *versus* 0.34 (0.12) post, $P < 0.001$). Elevations of TIMP-1 (0.72 (0.23) pre *versus* 1.44 (0.60) post, $P < 0.01$) and MMP-2 were also observed (0.03 (0.04) *versus* 0.12 (0.14), $P = 0.07$). The addition of Rapa was associated with similar changes to iNOS, TIMP-1 and MMP-2. However there was increased expression of TIMP-2 (0.30 (0.13) pre *versus* 0.55 (0.33) post, $P < 0.05$ and Collagen III (0.52 (0.16) pre *versus* 0.95 (0.43) post, $P < 0.05$) as well as an attenuation in the reduction of TGFβ expression seen with CyA reduction alone (0.32 (0.13) pre *versus* 0.32 (0.18) post).

Conclusion: Although CyA reduction alone decreased TGFβ and increased iNOS expression, elevation of TIMP-1 and MMP-2 expression suggest a persistent increase in the turnover of extracellular matrix. The addition of Rapa was associated with an increase in profibrotic gene expression. This provides a molecular explanation for the continued deterioration in renal function in patients taking rapamycin.

Moynihan 006

Magnetic resonance imaging quantification of external anal sphincter atrophy

A.B. Williams, C.I. Bartram, D. Modhwadia, T. Nicholls, S. Halligan, M.A. Kamm, R.J. Nicholls and W.A. Kmiot

St Mark's and St Thomas' Hospitals, London

Aims: Sphincter atrophy on endocoil MRI has been associated with poor results from sphincter repair, however, in the presence of a sphincter defect, no quantitative assessment of sphincter muscle quality exists. This study aimed to quantify external anal sphincter quality and atrophy on endocoil MR imaging using electromyographic assessment to confirm the presence of sphincter atrophy.

Methods: Women with intact sphincter muscles on endosonography (AES) and with a normal squeeze pressure (greater than 60 cm H_2O) ($n = 9$) or low pressure ($n = 16$), had endocoil MRI and electromyography. The area and fat content of the external anal sphincter and puborectalis were measured on mid-coronal MRI and images were graded as normal, intermediate or atrophic using electromyographic assessment of sphincter re-innervation as an indication of sphincter atrophy.

Results: Women with a normal and pressure had external sphincters that were larger in cross-sectional area (240 mm^2 (±56) *versus* 193 mm^2 (±62), $P = 0.01$) and had a lower mean fat content (23 per cent (±4) *versus* 29.7 per cent (±6) $P < 0.001$) than women with low squeeze pressure. Squeeze pressure correlated with cross-sectional sphincter area ($r = 0.32$, $P = 0.02$) and inversely with sphincter fat content ($r = -0.51$, p less than 0.001).

Conclusions: Endo-coil MRI can quantify sphincter atrophy and measurements made using this technique correlate well with squeeze pressure in patients with an intact external anal sphincter. Endo-coil MR imaging may be useful in selecting those patients with a sphincter defect who will most benefit from a sphincter repair.

ASGBI: Emergency/General 1–9

Thursday 26 April 2001 09:15–10:45

Emergency/General 001

Planned relaparotomy or relaparotomy on demand for secondary peritonitis

M A. Boermeester, E Belt, M J. Lubbers, J Kesecioglu, D J. Gouma and H Obertop

Departments of Surgery and Intensive Care, Academic Medical Center, Amsterdam, The Netherlands

Aims: The surgical treatment strategy of secondary peritonitis is still an unresolved issue largely due to lack of sufficient data In similar clinical situations, some surgeons perform a planned relaparotomy after 1 or 2 days, while others only perform a relaparotomy when the patient deteriorates or shows lack of improvement Many patients undergo multiple (planned) laparotomies for peritoneal lavage accompanied by a high risk of complications, although there are insufficient data to indicate which policy indeed contributes to recovery and survival We addressed this dilemma in our own series

Methods: The clinical data of 235 patients who received an emergency laparotomy for secundary peritonitis were examined retrospectively Mortality and morbidity results of 148 patients receiving at least one relaparotomy were analyzed by comparison of planned relaparotomy (PR, $n = 77$) and relaparotomy on demand (OD, $n = 71$)

Results: An increased mortality was found for the PR group compared to the OD group (34 2 per cent *versus* 26.8 per cent, logrank $P = 0\ 055$); which was predominantly seen in the APACHE II category of 11–20 points (admission score) Surgical complications (fistula, abscess) tended to be more frequently found in the OD group, although no difference was found for incisional hernia as a long-term complication.

Conclusions: Our data indicate a tendency towards an increased mortality after planned relaparotomy, although surgical complications may be increased after relaparotomy on demand. To obtain long-awaited prospective data, we have started a multicentre, randomized trial comparing these two surgical treatment strategies

Emergency/General 002

Xanthine oxidase as a diagnostic marker of acute intestinal ischaemia

C Stinchcombe,[1] M. France,[2] J. Hill[1] and R C. Pearson[1]

[1]*Departments of Surgery and* [2]*Pathology, Manchester Royal Infirmary*

Aims: Acute intestinal ischaemia is difficult to differentiate from other causes of acute abdominal pathology Xanthine oxidase (XO) activation may be an initiating factor in the multiorgan failure that follows gut ischaemia and gut ischaemia/reperfusion injury but there is a paucity of studies in humans. However, animal studies have shown that the enzyme xanthine dehydrogenase (XD) is present in high concentrations in intestinal mucosa and that during ischaemia, XD is converted to XO, which then enters the portal, and ultimately the systemic circulation.

Methods: We have compared serum assays of XO and XD in patients presenting with acute abdominal pathology without overt intestinal ischaemia, and in patients with proven full-thickness intestinal ischaemia

Results: In patients with intestinal ischaemia XO levels (mean 1.45, range 1 2–1.9, $n = 7$) were significantly higher than in patients with non-ischaemic pathologies (mean 0 31, range 0–1 58, $n = 73$, $P < 0.01$) and conversely XD was significantly lower in ischaemia (mean 0.095, range 0–0.642) than in non-ischaemia (mean 0.54, range 0–1.434, $P < 0\ 01$) Within the non-ischaemic group, patients with two or more Systemic Inflammatory Response Syndrome (SIRS) criteria had XO and XD levels that were significantly higher (mean XO 0 58, XD 0.74, $n = 40$) than those with 0 or 1 mean XO 0.07, $P < 0\ 01$, XD 0.30, $P < 0.05$, $n = 33$)

Conclusions: XO is present in the plasma in wide range of acute intra-abdominal conditions, particularly in the presence of inflammation, but in significantly greater amounts in patients with intestinal ischaemia In contrast to all other conditions, levels of XD in patients with intestinal ischaemia is low and the balance of XO and XD may allow development for the first time of a biological marker of full-thickness intestinal ischaemia

Emergency/General 003

Emergency surgery for intestinal obstruction in advanced malignancy

C.H. Wakefield,[1] S. Lo, I. Pope, D.W. Hamer-Hodges and R.G. Wilson

[1]*Department of Clinical and Surgical Sciences, University of Edinburgh and the Department of Surgery, Western General Hospital, Edinburgh*

Aims: Intestinal obstruction in patients with advanced malignancy is a common condition resulting in significant morbidity, and historically, surgical intervention is associated with an unacceptable mortality with only marginal clinical benefits This paper examines current surgical practice and its results for this difficult oncological emergency.

Methods: A retrospective cohort study of patients who underwent emergency surgery for intestinal obstruction in the presence of advanced metastatic malignancy. Patients were identified from prospectively collected databases over a 5-year period Principal outcome measures were operative mortality, overall survival and symptom control

Results: A total of 76 patients were identified with a median age of 66 (23–90) years. The commonest disease primary was colorectal (54 per cent), followed by gynaecological malignancy (15 per cent) Forty-seven (62 per cent) of patients had undergone surgical treatment of their primary, 23 (30 per cent) had chemotherapy and eleven (15 per cent) radiotherapy at a median interval from treatment to obstruction of 17, 7 and 19 months, respectively. At laparotomy a benign cause for obstruction was identified in seven (9 per cent) patients, multiple obstructing metastases in 51 (67 per cent) and an obstructing primary with advanced peritoneal disease in 16 (21 per cent) In only five (6 per cent) of cases was the laparotomy nontherapeutic, the remaining patients undergoing intestinal resection (51 per cent), bypass (18 per cent), defunctioning stoma (18 per cent) and adhesionolysis (5 per cent) Median postoperative stay was 14 (8–39) days, 30 day mortality 16 per cent ($n = 12$) with an in hospital mortality of 28 per cent ($n = 21$). Median survival following laparotomy for obstruction was 6 months 95 per centCI (3–9), Cox's proportional hazard model identified previous radiotherapy and nontherapeutic laparotomy to be independently associated with poor postoperative outcome (median survival, 75 v 260 days, $P = 0\ 02$ and 32 v 212 days, $P = 0.002$, respectively) Seven patients (10 per cent) developed further obstructive symptoms following their therapeutic laparotomy.

Conclusions: With current perioperative care, operative intervention for intestinal obstruction in the presence of advanced malignancy is no longer associated with prohibitive mortality If some form of palliative procedure is feasible, substantial obstruction-free survival is attainable.

Emergency/General 004

Is emergency surgery a major factor influencing postoperative mortality for colorectal cancer: results of a confidential enquiry

P Safranek, N. Bell and J A E. Smith, on behalf of the Wessex Colorectal Cancer Post Operative Mortality Review Group

South & West Cancer Intelligence Unit, Highcroft, Winchester SO22 5DH, UK

Aims: To reduce the postoperative mortality for colorectal cancer through confidential peer review and by identification of factors contributing to death at a clinical and organizational level locally

Methods: Representatives from 11 Trusts in the Wessex region formed a multidisciplinary steering group. All surgeons participated, reporting postoperative deaths from colorectal cancer between April 1st 1999 and March 31st 2000. Proformas collected information on admission, pre-operative work up, anaesthesia, surgery and postoperative care. Anonymized sets of material were reviewed by two independent surgeons, a pathologist and anaesthetist and the reviews discussed by the steering group chairman (a pathologist), a surgeon and a public health physician

Results: One hundred and four cases were identified and data received on 97 (93 per cent) Although 38 (39 per cent) were admitted as an emergency only seven (7 per cent) had emergency surgery and 39 (40 per cent) urgent surgery (within 24 h of resuscitation) 22 of the emergency/urgent cases (48 per cent) had a consultant present compared to 44 (86 per cent) of elective cases The consultant made the decision to operate in only 41 (89 per cent) of emergency/urgent cases compared to 51 (100 per cent) of elective cases In 26 (57 per cent) of emergency/urgent cases the surgical consultant was a colorectal specialist compared to 42 (82 per cent) of elective cases Factors identified included insufficient preoperative work up (26 per cent of emergency/urgent cases and 11 per cent of elective), availability of ITU for patients with serious comorbidity, consider stenting, poor death certificate information and appropriateness to operate on 85+ year-olds with serious comorbidity

Conclusions: Whilst 39 per cent of cases were emergency admissions, only 7 per cent had emergency surgery which is therefore not a major factor. However 40 per cent underwent urgent surgery and attention needs to focus on preoperative assessment, of these cases, to determine comorbidity and stage of disease which would contribute to the decision on appropriateness of operation on patients with serious comorbidity and the need for ITU support.

Emergency/General 005

Emergency surgery in octogenarians: what is the long-term outcome?

A.R. Carmichael, C.M. Butler, R.W. Hoile and P. Webb
Medway Maritime Hospital, Windmill Road, Gillingham, Kent ME7 5NY

Aims: To study the long-term outcome in octogenarian patients after emergency surgical intervention in terms of survival and quality of life (QOL).
Methods: Retrospective review of 128 emergency surgical admissions during 1996. The data were collected in terms of clinical and operative factors as described in POSSUM. Long-term survival figures were obtained from hospital PAS system and GP records. QOL studies are being conducted at present.
Results: Of 128 emergency surgical admissions 109 (85 per cent) notes were retrieved and reviewed. Sixty-seven (52 per cent) patients were managed conservatively and 41 (48 per cent, 23F:18M) underwent a surgical procedure. Major abdominal surgery was performed in 29 (70 per cent) patients. Median age at the time of surgery was 84 years. Median (range) American Society of Anesthesiologist Score was 2 (1–4). Mean duration of operation was 80 min. Total physiology severity score was 32 and total operative severity score was 20. The percentage risk of death by POSSUM score was 58 per cent. Thirty-day was 30 per cent. A significant post-operative morbidity was experienced by 15 per cent of patients. Median (range) survival was 8 (0–39) months. Twelve (30 per cent) of patients were alive 2 years after surgery. Two of these patients were demented and required full-time nursing care. QOL study results will be added for presentation.
Conclusions: It is possible to carry out emergency surgical procedure in octogenarian patients with acceptable morbidity and mortality, however, long-term survival in the octogenarian population is poor.

Emergency/General 006

Management of the minor surgical emergency workload by specialist nurse pre-assessment and co-ordination

M. Radford, P. Johnston, A. Williamson and A. Jewkes
Departments of Surgery & Anaesthesia, Good Hope Hospital NHS Trust, Sutton Coldfield

Aims: The emergency surgical workload is increasing and within this workload there is a proportion of 'minor' surgical procedures, that are often cancelled or postponed due to more immediate or life-threatening emergencies. There is a role for a specialist nurse to co-ordinate this workload with medical staff to ensure rapid access to available theatre space after appropriate pre-operative assessment and optimization.
Methods: Using the BUPA classification of 'minor' procedures, emergency surgical workload during a 3-month period (May–July 1999) was identified retrospectively. This was compared with audit data from a matched period (May – July 2000) collected following the creation of a Specialist Nurse role. An analysis was performed to assess the level of cancellations and length of hospital stay after creation of the post.
Results: Between May–July 2000, 111 minor procedures were performed, comprising 30 per cent of the total number of emergencies. After booking, only 23 per cent of patients were delayed to the following day, compared to 50 per cent in the previous year, a reduction of 52 per cent. 97 per cent of minor cases were completed within 24 h following surgical decision to operate compared with 83 per cent in the previous year; no patient waited longer than 36 h. Of those patients formally assessed by the Specialist Nurse, 45 per cent were discharged within 24 h, of which 15 per cent were completed and discharged on the same day utilizing the day case unit. 21 per cent were redistributed to alternative theatres. 94 per cent of patients assessed by the nurse had their operation completed on the same day, with mean time from assessment to surgery of 2.6 h.
Conclusion: The minor surgical caseload forms a large part of the surgical workload and can be effectively co-ordinated by a specialist nurse. This approach improves overall theatre utilization, reduces cancellations and frees valuable bed stock by improving discharge for this patient group.

Emergency/General 007

Problems of emergency vascular practice in a geographically peripheral District General Hospital

S. Shiralkar, D. Schrimph and W.V. Humphreys
Ysbyty Gwynedd Hospital, Bangor

Introduction: The ideal service delivers vascular expert care 24 h/day. In reality, vascular services in many areas are haphazard and unplanned. Many hospitals are served by only one or two vascular surgeons who individually cannot provide a comprehensive emergency rota. Their general surgical colleagues are increasingly reluctant to take on these difficult cases in their absence, and surgeons should not be expected to perform emergency operations that they do not regularly perform electively.
Aims: To audit the problems of an emergency vascular practice without external cross cover in a geographically peripheral DGH.
Methods: This will be a prospective study of all emergency vascular admissions from 15 February 2000 to 15 October 2000 in a DGH where there are two vascular/general surgeons providing vascular service. In this particular period a senior vascular surgeon happened to be away for the first three months (15 February to 10 May) of this study period and the second surgeon was away for a month. All the emergency vascular admissions were entered on a database, including their investigations and treatment and were analysed.
Results: This is an ongoing study. A total of 48 emergency vascular admissions from 15 February to 15 May were audited. These were part of a total of 512 general surgical admissions (9.4 per cent). During the period without vascular cover, some 17 cases had to be transferred to geographically distant centres. This caused delay in the management of several patients. The outcome of these patients will be further analysed and compared with patients in a period when full vascular cover has resumed.
Conclusions: There should be a 24-h vascular service delivering optimal patient care.

Emergency/General 008

Co-ordination of the emergency surgical workload by specialist nurse pre-assessment: the effect on emergency theatre operating patterns

M. Radford, P. Johnston, A. Williamson and A. Jewkes
Departments of Surgery & Anaesthesia, Good Hope Hospital NHS Trust, Sutton Coldfield B75 7RR, UK

Aims: The role of a specialist nurse who co-ordinates emergency theatre workload can impact positively on the efficiency of this service. The role involves pre operative assessment, and appropriate optimization of the patient's condition, along with prioritisation with medical staff and possible redistribution to available theatre space
Methods: A regular audit programme has been in place in the emergency operating theatre (EOT) since 1996, examining utilisation, activity and delays. Detailed comparative analysis of these markers was performed after the creation of the specialist nursing role in May 2000, compared with a matched period in the previous year.
Results: Between 8 am and 10 pm, EOT utilisation has risen from 37.2 per cent in 1996 to 73 per cent in 2000, concomitant with a 17 per cent rise in activity during the same period. Following the start of the Specialist Nurse post the EOT has started before 10:30 am on 77 per cent of days compared to 68 per cent in the previous year. 88 (9 per cent) patients booked in EOT were redistributed to 'elective' operating sessions. There has been a 30 per cent reduction in 'on-call' operating time between 10 pm and 8 am, along with a 30 per cent reduction in the total number of patients operated on in this time period. This strategy has also seen a 17 per cent reduction in the total hours of delays in the EOT.
Conclusions: Emergency surgical workload can be effectively co-ordinated by a specialist nurse, whose role supports consultants and junior medical staff in managing the emergency patient. It also improves overall theatre utilization and efficiency by the redistribution of workload, the reduction of delays, plus reducing the burden of 'on-call' operating for junior and consultant medical staff.

Emergency/General 009

Percutaneous endoscopic gastrostomy: 5 years experience in 238 patients

J.J. Sheehan, N.P. Fanning, C. Healy, N.J. O'Higgins, E.W. McDermott, D.P. O'Donoghue and A.D.K. Hill

Surgical Professorial Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

Introduction Since the inception of PEG feeding 20 years ago its utilization has continued to increase leading to concern regarding its overutilization, however, PEG feeding facilitates nursing care in patients unable to tolerate oral feeding. The aim of this study was to assess the current indications and complications associated with PEG and to evaluate the concern regarding overutilization.

Methods: We performed a 5-year retrospective review of PEG tube placement in a university teaching hospital during the period January 1995 to March 2000. Two hundred and thirty-eight patients had attempted PEG tube placement, of which adequate follow up records were available for 205 (84 per cent). Of these 193 (94 per cent) had successful placement

Results: The number of PEG tubes inserted has increased annually from 37 in 1995 to 65 in 1999. The indications for insertion were for central nervous disease 76 per cent ($n = 156$), other benign lesions 14 per cent ($n = 28$) and malignant lesions 10 per cent ($n = 21$) Cerebrovascular accidents (CVA) alone accounted for 47 per cent ($n = 97$). There were four deaths (2 per cent) related to PEG placement, which included three aspiration pneumonias and one case of peritonitis. There were six (3 per cent) major complications, which included peritonitis, perforation and aspiration pneumonia Ninety-seven (50 per cent) patients had minor complications, which included 33 (17 per cent) tube leakages, 43 (22 per cent) wound infections and five (3 per cent) aspiration pneumonias. There were 14 (6 per cent) failed insertions and 12 (6 per cent) occlusions. Twenty-nine patients (15 per cent) required the PEG to be replaced. The overall 30 day mortality rate was 16 per cent There was a 20 per cent 30-day mortality ($n = 19$) in the CVA group compared to 11 per cent ($n = 11$) in the non-CVA group which was felt to reflect the nature of the disease and not the procedure itself

Conclusion Percutaneous endoscopic gastrostomy has a morbidity of 53 per cent and a mortality of 2 per cent, however, we feel that the increasing use of PEG feeding is justified given its benefits to patients and nursing staff.

ASGBI: Six of the best UGI/HPB — Thursday 26 April 2001 09:45–10:45

UGI/HPB 001

Bleeding peptic ulcers – fifteen years of emergency surgery

T.J. Wheatley, L. Hunt and D.F.L. Watkin

Leicester Royal Infirmary, Leicester

Aims: The number of emergency operations performed for bleeding peptic ulcers has decreased over the last 10 years. This study set out to review both the number and nature of such procedures in a single centre over a 15-year period.

Methods: Records on all patients who underwent emergency surgery for bleeding peptic ulcers at Leicester Royal Infirmary from 1984 to 1998 were identified from a computerized database. Casenotes and computer records were reviewed to establish patient demographics, type of ulcer, prognostic factors (using the Rockall scoring system), operative procedures, morbidity, and mortality rates. Data obtained were divided into three 5-year blocks for comparison.

Results: Two hundred and forty-one operations were performed; 108 from 1984–1988 (group A), 88 from 1989–1993 (group B), and 45 from 1994–1998 (group C). Age and sex distributions were similar between the three groups. Duodenal ulcers were more common than gastric ulcers, accounting for 57 per cent overall (62 per cent group A, 50 per cent group B, 58 per cent group C). Rockall scores were not available for group A, but were similar for groups B and C (median value 6 and 5, respectively).

Operation	Group A (DU:GU)	Group B (DU:GU)	Group C (DU:GU)
Local (suture/excision)	4 (1:3)	36 (18:18)	32 (14:18)
Vagotomy and drainage	70 (58:12)	31 (21:10)	2 (2:0)
Gastrectomy	33 (7:26)	20 (5:15)	11 (10:1)
None	1 (1:0)	1 (0:1)	0 (0:0)

Serious complications affected 29 per cent, 28 per cent, and 49 per cent of patients in groups A, B, and C; and mortality rates were 21 per cent, 18 per cent, and 29 per cent, respectively.

Conclusions: The number of patients requiring emergency surgery for bleeding ulcers has more than halved, and the choice of operation has moved to a more conservative approach, reflecting the influence of improved medical management of peptic ulcer disease. Morbidity and mortality rates have risen, due possibly to a preselected group of higher-risk patients, and relative unfamiliarity with the surgery.

UGI/HPB 002

Urgent laparoscopic cholecystectomy for acute biliary disease: a prospective study

V.S. Menon, A. Masoud, C.P. Gibbons, J.N. Baxter and T.H. Brown

Department of Surgery, Morriston Hospital, Swansea SA6 6NL, UK

Aims: This study was performed to assess the outcome of laparoscopic cholecystectomy (LC) for acute biliary disease including the difficulties encountered, complications and conversion rate. We also analysed the prevalence of acute cholecystitis (AC), biliary colic (BC), gall stone pancreatitis (GSP), and calculous obstructive jaundice (COJ) in these patients.

Methods: Patients admitted as emergencies referred to three consultants were offered urgent LC during that admission, if fit. Surgery was usually performed on a CEPOD list (AC/BC), after ERCP (if needed), or when the pancreatitis had settled.

Results: Over 15 months 120 patients underwent urgent LC; 85 females and 35 males with a median age of 51 years (range 21–82). The incidence of AC was 57 (47 per cent), BC 26 (21 per cent), GSP 28 (24 per cent), COJ eight (7 per cent) and one (1 per cent) in three categories. AC diagnosis was based on presentation and histology and included 11 with a necrotic gallbladder. 83 patients had AC or BC, of which 40 had leucocytosis, 19 were pyrexial, 14 had raised LFTs and 41 had radiological evidence of AC. The median operating time was 65 min (range 35–180), and the complication rate was 8.3 per cent (three with retained stones, two minor bile leaks, two urinary retention, one umbilical port site herniation, one umbilical infection, and one pulmonary embolism). The conversion rate was 13.3 per cent ($n = 16$), 21.4 per cent in GSP and 17.5 per cent in AC, and none in BC and COJ. Gall bladder aspiration was needed in 30, abdominal drain in 85, cystic duct loop/suture in 10 and fundus first dissection in four patients. Difficulty was recorded on a linear scoring system and 67 (55 per cent) seemed difficult. There was no mortality or any major bile duct injury.

Conclusions: Urgent LC during acute admission can be safely performed with an acceptable conversion and complication rate. A major advantage is to prevent recurrent attacks while awaiting routine surgery.

UGI/HPB 003

Gastric colonization, intestinal permeability and septic morbidity in acute pancreatitis

C.E. McNaught, N. Woodcock, C.J. Mitchell and J. MacFie

Combined Gastroenterology Unit, Scarborough Hospital, UK

Aims: Bacterial translocation of enteric organisms may promote septic morbidity in acute pancreatitis. The aim of this study was to assess proximal GI colonization and intestinal permeability in patients with acute pancreatitis and relate this to disease severity and outcome.

Methods: Within 24 h of admission, patients with acute pancreatitis had a nasogastric aspirate taken for microbiological assessment. Intestinal permeability was measured using a dual sugar probe technique (lactulose/rhamnose). Disease severity was recorded using the modified Glasgow (Imrie) scale. Septic complications were documented prospectively.

Results: Of the 55 patients entered into the study, 20 (36 per cent) had severe disease and 35 patients (64 per cent) had mild disease. 43/53 (81 per cent) nasogastric aspirates were culture-positive. There was a significantly higher incidence of enteric organism colonization in patients with severe disease than with mild disease (10/20 *versus* 3/33, $P < 0.001$). Mean intestinal permeability was higher in the severe group (0.189, $n = 6$) than in the mild group (0.080, $n = 19$). In the severe group, 6/20 patients developed one or more septic complication compared to 4/35 patients in the mild group. This difference failed to reach statistical significance ($P = 0.14$). Patients in the severe group had a significant increase in mortality (4/20 *versus* 0/35 $P = 0.01$).

Conclusions: Gastric colonization with enteric organisms is significantly increased in patients with severe pancreatitis and is associated with an increased level of septic morbidity and mortality.

UGI/HPB 004

The role of diet in the development of Barrett's oesophagus and oesophageal adenocarcinoma

A.M. Harris,[1] C. Seal,[1] N. Hayes and S.M. Griffin

Northern Oesphago-Gastric Unit, Royal Victoria Infirmary, Newcastle upon Tyne, and [1]Department of Biological and Nutritional Sciences, University of Newcastle upon Tyne, UK

Aims: The incidence of oesophageal adenocarcinoma is rising at a rapid rate, the reason for which is as yet unexplained: it may be due to dietary habits, but very few studies have investigated this to date. The aim of this study therefore was to evaluate dietary history in these patients and those with Barrett's oesophagus, the precursor lesion, in order to and identify possible dietary factors that may be implicated in the development of these diseases.

Methods: Patients with histologically confirmed oesophageal adenocarcinoma ($n = 100$), Barrett's oesophagus ($n = 100$) and age- and sex-matched controls ($n = 109$) completed a detailed food frequency questionnaire that utilizes photographs of food portions to increase data accuracy; BMI and lifestyle data were also collected. Dietary data were processed by specialized software (Integrated Dietary Analysis^{TM}) to produce a comprehensive nutritional breakdown of each individual's diet, and subsequent statistical analysis was performed using analysis of variance and Tukey *post hoc* for multiple comparisons.

Results: Initial analysis revealed no significant differences between groups for absolute intake of the major food groups, however, the percentage of the total energy intake derived from fats was increased in the cancer group compared with controls ($P = 0.031$), and in particular monounsaturated fats ($P = 0.007$); percentage energy from carbohydrates was correspondingly lower in the cancer group *cf* controls ($P = 0.047$). In addition there was reduced intake of vitamin C in both the cancer group *cf* controls ($P = 0.016$) and Barrett's group *cf* controls ($P = 0.007$): other factors bordering on significance included lower percentage energy from protein in cancers *cf* Barrett's, reduced intake of dietary fibre in cancers and Barrett's *cf* controls, lower Pantothenic acid in cancers *cf* Barrett's, and lower carotene in Barrett's *cf* controls.

Conclusions: This study suggests that diet may play an important role in the development of both Barrett's oesophagus and oesophageal adenocarcinoma, particularly in relation to intake of fats and vitamin C. The association with other micronutrients is more equivocal, but the aetiology is likely to be multifactorial and further studies are needed to confirm these findings.

UGI/HPB 005

Survival, quality of life and quality-adjusted survival of patients in the ESPAC-1 trial: a European randomized trial to assess the roles of adjuvant chemotherapy and chemoradiation in resectable pancreatic cancer

J.P. Neoptolemos, D.D. Moffitt, J A Dunn, J Almond, H G Beger, K H. Link, P Pederzoli, C. Bassi, C Dervenis, L Fernandez-Cruz, F. Lacaine, D Spooner, D J Kerr, H Friess and M W Buchler

C R C Trials Centre, Royal Liverpool University Hospital, Liverpool, UK

Aims: To assess the roles of adjuvant chemotherapy and chemoradiation in resectable pancreatic cancer

Methods: ESPAC-1 is the largest randomized adjuvant pancreatic study aiming to answer two questions (i) is there a role for chemoradiation (40Gy + 5-fluorouracil), (ii) is there a role for chemotherapy (5-fluorouracil + folinic acid). 541 patients with pancreatic ductal adenocarcinoma were randomized from 83 clinicians in 11 countries. Quality of life (QoL) was assessed by patient questionnaires (EORTC QLQ-C30/ESPAC-QLQ32) completed at 3-monthly intervals. Additional QoL-related information was collected by the clinician (performance status, weight, diabetes and enzyme supplements). Changes in dimension scores within 6 months from entry were compared between treatments. Calculation of the quality adjusted life months (QALM) for the global QoL score enabled the length of survival and QoL to be combined

Results: Two hundred and twenty-seven patients (42 per cent) are alive with median follow-up of 10 months (interquartile range 1–25). Preliminary results show no evidence of a survival benefit for chemoradiation treatment (median survival 15.5 months with chemoradiation *versus* 16.1 months without, $P = 0.24$). There is evidence of a benefit for patients having chemotherapy (median survival 19.7 months with chemotherapy *versus* 14.0 months without, $P < 0.001$). A total of 296 patients have completed 789 QoL questionnaires within 1 year of entry. Initial analysis suggests there is a slight detriment with chemotherapy for social functioning ($P = 0.03$), role functioning ($P = 0.02$) and constipation ($P = 0.05$), within the 6 months from entry. However, with adjustment for multiple comparisons these differences become non-significant ($P > 0.05$). There are no significant differences in the QALM between either treatment comparisons within the first 12 months from entry to trial (no chemotherapy *versus* chemotherapy, $P = 0.37$, no chemoradiation *versus* chemoradiation, $P = 0.61$)

Conclusions: Chemotherapy may have some benefit in terms of survival but there was no survival benefit with adjuvant chemoradiotherapy. There were no significant differences in terms of QoL and QALM between treatments within 6 months and 12 months from entry

UGI/HPB 006

A one-year survey of carcinoma of the oesophagus and stomach in Wales

R R Pillarisetti, R. Kerwat, J. Charles, A. Biffin, M E Foster, J.K Pye and M KH Crumplin

Wrexham Maelor Hospital, Wrexham, UK

Aims: To identify all patients presenting with oesophagogastric malignancy within a single NHS region (Wales) over 1 year, and to follow the cohort for 5 years. Management and outcome were analysed to identify current practice and to draft Welsh guidelines

Methods: Patients were identified from hospital records. Details were recorded in structured format for analysis.

Results: Analysable data were obtained on 910 of 916 patients. The overall incidence was 31 4 100 000. Treatment was by resection 298 (32.7 per cent), palliation 397 (43.6 per cent) or no treatment 215 (23.6 per cent). 30-day mortality was 12 per cent and in-hospital mortality 13 per cent. There were 226 (25 per cent) alive at two years. Resection conferred a significant survival advantage over palliation ($P < 0.001$), and no treatment. Anastomotic leakage occurred in 16 (5.4 per cent) with 50 per cent mortality. 'Open and close' operations were frequent (23 per cent), laparoscopy was infrequent (16 per cent), and many surgeons undertook small caseloads. Operating on <6 cases per year increased mortality after partial gastrectomy ($P < 0.05$), and a trend to higher mortality after mediastinal and cardia surgery. Operating on >70 per cent of cases seen, resulted in significantly higher mortality ($P = 0.0004$) irrespective of case volume.

Conclusions: Tumour resection conferred a survival advantage. Wider use of laparoscopy is advocated and improved selection for surgery should result in lower mortality

ASGBI: Endocrine/Breast 1–6 Thursday 26 April 2001 11:15–12:15

Endocrine/Breast 001

Caspase and cytochrome C induction in thyrocyte apoptosis

F.F. Palazzo, L.J. Hammond, R. Mirakian and A.W. Goode

St Bartholomew's and Royal London Hospitals Medical School, London, EC1A 7BE

Introduction Thyrocyte apoptosis is controlled by pro-apoptotic pressures (Fas/FasL, TNF/TNFR, etc.) and survival factors (Bcl-2 family). In Hashimoto's thyroiditis (HT) deregulation of proapoptotic gene expression is thought to be responsible for thyrocyte apoptosis.

Aims: (1) To evaluate constitutive caspase and cytochrome C activation in patients with and without autoimmune thyroid disease; (2) to assess the effect of plasma containing autoantibodies and a cytokine environment on caspases and Bcl-X in thyrocytes.

Methods: Thyrocyte culture with plasma from patients with HT, Graves' disease (GD) and multinodular goitre (MNG) and cytokines for varying time intervals followed by Western blot evaluation of thyrocyte caspase 8, 3, cytochrome C expression. Bcl-X expression was studied in 10 MNG, 10 GD and 4 HT thyroids by immunofluorescence (and quantified with confocal microscopy) and by Western blot.

Results: Human plasma up-regulates caspase 8, 3, and cytochrome C in thyrocyte cultures with no differential effect between plasmas from patients with and without autoimmune thyroiditis. Bcl-X is constitutively under-expressed in HT and down-regulated by pro-inflammatory cytokines.

Conclusions: Heat-stable constituents of normal human plasma may provide a constant pro-apoptotic stimulus to thyrocytes suggesting that *in vivo* specific caspase inhibitors operate to prevent the activation of the caspase cascade. In HT pro-inflammatory cytokines released by activated T cells would be responsible for the impairment of Bcl-X expression on thyrocytes and this in combination with the failure of the caspase inhibitory system would be responsible for thyrocyte apoptotic death.

Endocrine/Breast 002

Evidence of an early angiogenic switch in parathyroid glands

L.P. Marson, K.M. Kurian,[1] K. McLaren,[1] O.J. Garden and J.L.R. Forsythe

Departments of Clinical and Surgical Sciences and [1]Pathology, Royal Infirmary of Edinburgh, UK

Aims: The ability of hyperplastic parathyroid glands to function following excision and subsequent implantation into forearm muscle is unique and must depend on development of a new blood supply. The aim of the study was to examine angiogenesis in normal, hyperplastic and adenomatous parathyroid glands to determine whether there is a progressive change in new vessel formation.

Methods: Tissue sections from 14 patients with hyperparathyroidism secondary to chronic renal failure were studied. Five patients who had undergone excision of parathyroid adenoma and a section of normal gland were included. Following staining of sections with the endothelial cell marker, antibody to CD31, microvessel counts (mvc) were performed by two observers using a Chalkley eyepiece graticule. Observers were blinded with respect to the histology of sections. Statistical analysis was performed with the SPSS program version 9.0 using Mann–Whitney test to compare counts in normal, hyperplastic and adenomatous glands.

Results: The range of mvc across all groups was 3–44.

MVC	Normal ($n = 5$)	Hyperplastic ($n = 14$)	Adenoma ($n = 5$)
Range	3–11	12–44	12–33
Median	9	24.5	31
Mean	7.4	25	25.6

Normal *versus* hyperplastic, $P = 0.001$, hyperplastic *versus* adenoma, $P = 0.6$, normal *versus* adenoma, $P = 0.001$.

Conclusions: The study demonstrates a switch to the angiogenic phenotype in hyperplastic parathyroid glands, which is earlier than the switch described during the preinvasive stage of tumour development. These novel findings may explain the ability of parathyroid glands to function following excision and implantation into forearm muscle and provide a new clinical model of angiogenesis.

Endocrine/Breast 003

Mode of presentation and outcome in patients with multiple intraductal papilloma (MIP) or papillomatosis of the breast

S. Prance, S. Dutta, L. Campbell, P.A. Jones, D.M. Lee, R.M. Watkins and C. Teasdale

Department of Surgery, Radiology and Pathology, Derriford Hospital, Plymouth

Aims: The risk of concurrent or subsequent malignancy in patients with MIP or papillomatosis is uncertain. The presentation and short-term outcome of 35 patients with MIP in a symptomatic Breast Unit was studied.

Methods: Thirty-five patients diagnosed as MIP between 1988 and 1999 were studied retrospectively. The patient profile, mode of presentation, radiological and pathological characteristics have been reviewed.

Results: The age range was 21–69 (mean 47.5 years). 18 patients were symptomatic (14 had a lump, three had nipple discharge and one had both). Mammogram and/or ultrasonography was performed in 16 patients. Three were malignant (R5), four were R4/U4, two were U3, five benign, one had microcalcification and one was a lobulated opacity. Seventeen patients presented with a mammographic abnormality alone (10 with microcalcification, three with a mass lesion, two with cysts, one with a stellate lesion and one with multiple densities). Three out of 18 patients (16.7 per cent) in the symptomatic group and eight out of 17 with mammographic abnormality (47.1 per cent) had in-situ or invasive cancer on final histology. 31 patients had excision biopsy, three had mastectomy or wide local excision and one had major duct excision. Follow-up over 1–8 years in four out of seven patients with family history of breast carcinoma detected no carcinoma. One out of five patients with atypical ductal hyperplasia had associated papillary malignancy and had two further carcinomas over a 9-year follow-up period. Two out of 11 patients with associated invasive ductal carcinoma or DCIS developed further carcinomas.

Conclusions: The long-term risk of developing malignancy in patients with MIP remains difficult to quantify. Careful excision and regular follow-up is recommended.

Endocrine/Breast 004

The role of intraoperative imprint cytology in determining the histological status of the sentinel lymph node

M. Keshtgar, A. Lee, I. Taylor, T. Davidson, P.J. Ell,[1] D. Ralphs[1,2] and G. Kocjan[3]

Department of Surgery, [1]Institute of Nuclear Medicine, [3]Department of Histopathology, Royal Free and University College Medical School, UCL, London and [2]Department of Surgery, Norfolk and Norwich NHS Trust, UK

Aims: The histological status of the axillary lymph node remains one of the most important prognostic indicators in breast cancer patients. It was the aim of this study to evaluate the accuracy of touch imprint cytology (TIC) as an intraoperative diagnostic tool to determine the histological status of the sentinel lymph node (SLN) in patients with invasive breast cancer.

Methods: Between September 1997 and February 2000, a total of 117 patients were enrolled in this study. The study was approved by the local ethics committees. The median age of the patients was 58 years (range, 34–83 years). After harvesting, the SLN was bisected and a clean glass slide touched onto the cut surface, resulting in cell imprints. Three slides were prepared per SLN and underwent rapid, definitive and immunohistochemical staining.

Results: A total of 141 SLN were biopsied from 117 patients (1.2 nodes per patient). The pathological diagnosis by TIC was accurate in 115 patients (98.2 per cent). In 30 patients there was evidence of metastatic deposit on definitive histology (25.6 per cent) and TIC correctly diagnosed this in 28 patients. There were no false-positive cases in this series. With two false-negative cases, the sensitivity of this technique was 93.7 per cent, the specificity was 100 per cent and the positive predictive accuracy, 100 per cent and negative predictive accuracy, 97.7 per cent.

Conclusions: TIC is a rapid and reliable intraoperative method for determining the histological status of the SLN in patients with breast carcinoma. It will enable the surgeon to decide on performing ALND at the time of initial surgery with acceptable accuracy. Immunocytochemistry may be used to improve diagnostic accuracy of this method.

Endocrine/Breast 005

CerbB2 oncoprotein expression is increased in breast cancer bone metastases

R A Linforth, N G Anderson, W F Knox and N J Bundred

Academic Department of Surgery, South Manchester University Hospital, UK

Aims: Type 1 tyrosine kinase receptors such as epidermal growth factor receptor (EGFR) and CerbB2 oncoprotein have been shown to predict for a poor prognostic outcome in early breast cancer (EBC), but the incidence of such receptors in breast cancer at metastatic sites is unknown. We determined the incidence of these receptors in breast cancer bone and visceral metastases compared to primary EBC

Methods: Using standard immunohistochemical techniques, the incidence of EGFR and CerbB2 expression was determined on sections of formalin fixed primary and metastatic breast tissue. Disclosure of the primary antibodies was performed with a swine antirabbit antibody, streptavidin and diaminobenzidine-hydrogen peroxide staining was classed as greater than 5 per cent of epithelia expressing the target antigen A positive control was used in each run and a control slide used for each test sample Scoring was performed by a single observer, and verified by an experienced pathologist Results were analysed using the χ^2 test

Results:

	CerbB2	EGFR
Bone metastases	11/21 (52%)*	6/21 (29%)
EBC	21/76 (28%)	25/70 (36%)
Visceral Metastases	9/22 (40%)	10/18 (55%)

Expression of CerbB2 oncoprotein was significantly increased in bone metastases, compared to EBC (*$P = 0.029$) The frequency of EGFR expression was highest in visceral metastases

Conclusions: The increased expression of CerbB2 oncogene in breast cancer bone metastases may explain the low response rate to hormonal therapy in bone and supports the rationale for biopsing bone metastases and the use of therapeutic anti-CerbB2 monoclonal antibodies for this condition

Endocrine/Breast 006

Sentinel lymph node biopsy in breast cancer – is lymphoscintigraphy really necessary?

S S Upponi[1] S A. McIntosh, G C Wishart, K K Balan[1] and A.D. Purushotham

Cambridge Breast Unit & [1]Department of Nuclear Medicine, Addenbrooke's Hospital, Cambridge

Aims: Lymphoscintigraphy is regarded as a useful tool in sentinel lymph node (SLN) biopsy in breast cancer The aim of this study is to ascertain its value in axillary SLN detection

Methods: Axillary SLN biopsy was undertaken using the combined approach of patent blue dye and gamma probe detection Lymphoscintigraphy was performed but the operating surgeon was blinded to the results of the lymphoscintigram Following SLN biopsy and prior to closure of the axillary wound the lymphoscintigram was reviewed Internal mammary node dissection is not performed in this unit

Results: Of 52 patients who underwent lymphoscintigraphy, 42 (81 per cent) had successful scans. Of these, 33 (79 per cent) had axillary nodes, four (10 per cent) internal mammary nodes and axillary nodes and fove (12 per cent) internal mammary nodes on lymphoscintigrams All of these patients had axillary sentinel nodes identified intraoperatively by gamma probe or visual detection of blue-stained lymphatics and node(s). Review of the preoperative lymphoscintigrams demonstrated that they would not have influenced intraoperative axillary SLN detection in any patient

Conclusions: Lymphoscintigraphy does not contribute to axillary SLN biopsy in women undergoing surgery for breast cancer

ASGBI: General 1–6 — Thursday 26 April 2001 11:15–12:15

General 001

Amount of water utilized for scrubbing. Is the cost and the quantity justified?

B. Patel, L.M. Awere and R.D. Rosin

St Mary's Hospital, Praed Street, London W2 1NY, UK

Aims: Evaluation of the quantity of water utilized and the costs associated with surgical hand scrubs.

Methods: The study was set in a university teaching hospital. This is a prospective blinded study where the subjects were not aware that they were timed during scrubbing. A total of 120 observations was made of operating theatre staff scrubbing before operations. Using a standard sports stop watch the time used for scrubbing (S^T) and time when hands were in contact with the running water (W^T) to wash the antimicrobial agent were calculated.

Results: S^T value varied from minimum of 2 min to a maximum of 7 min. W^T value varied from minimum of 19 s to a maximum of 124 s. The mean S^T vs. W^T values were calculated for each grade of theatre personal scrubbing before an operation. Consultants ($n = 16$) mean S^T vs. W^T value is 3.3 min vs. 37.4 s, registrar ($n = 29$) 3.3 min vs. 39.5 s, SHO ($n = 17$) 3.2 min vs. 37.8 s, JHO ($n = 6$) 3.8 min vs. 33.2 s and nurses ($n = 52$) 4.1 min vs. 48.5 s. Taking from an average of three readings of each low, medium and fast flow, volume per minute was calculated. At low water flow 2660 mL min^{-1} of water was running through the tap, at medium flow 3916 mL min^{-1} and at fast flow 9066 mL min^{-1}. The mean flow was 5214 mL min^{-1}e. The overall mean S^T was 18.3 L, and the overall mean W^T was 39.3 s. From these readings the actual volume of water necessary to wash the hands was calculated to be 3.4 L. The cost of water is 70.4 pence and sewage 50.8 pence per cubic metre (per 1000 litre). There were a total of 6927 operations performed in our hospital main theatre between 1/11/99 and 31/10/2000. Assuming an average of four theatre staff scrubbing for each case, the total quantity of water used for scrubbing will be 507 056.4 L annually where as only 94 207.2 L of water was actually necessary.

Conclusions: This is the first study in the literature evaluating the quantity of water utilized verses the quantity of water necessary for surgical hand scrubs (A mean of 18.3 L vs. 3.4 L). This can have a major implication on cost and quantity of water used in developing countries and in the setting up of operating theatre in geographic areas where water can be more costly than oil! We strongly recommend use of light-sensor activated water taps or an on/off foot pedal during scrubbing.

General 002

Evidence against the reliability of the inpatient case-note record as an accurate descriptor of the process of care

K.J. Fernando and A.K. Siriwardena

Department of Surgical and Clinical Sciences, Royal Infirmary of Edinburgh, Edinburgh, UK

Aims: Although current guidelines issued by the General Medical Council (GMC) state that all doctors should keep contemporaneous records of every consultation, the documentation of consultant surgical advice is often carried out by junior house officers. This study examines the accuracy of this traditional system of 'indirect' case-note record-keeping.

Methods: A prospective study was carried out in the General Surgical service of a university teaching hospital. Thirty-five consultant ward rounds comprising 432 surgeon-patient consultations constituted the study population. Information discussed during the surgeon–patient consultation was recorded in shorthand during the round. Data were recorded in the categories recommended by the GMC: clinical findings, decisions made, information given and treatment prescribed. Notes were examined within 24 h of the round (at the end of the working day) to ascertain what proportion of the consultants' recommendations had been documented. Data are expressed as medians (range).

Results: Overall clinical findings were recorded in 67 per cent (38–100) however, there were important deficiencies in documentation of surgically relevant facts (abdominal signs, vomiting, fever). Decisions regarding treatment were documented in 75 per cent (59–100). Again, there were important omissions. Information regarding diagnosis and treatment plan was recorded in only 14 (3 per cent).

Conclusions: This study provides objective evidence that inpatient case-note documentation is not an accurate descriptor of the process of care. Our findings have implications with respect to compliance with the GMC recommendations for case-note keeping and also in relation to medicolegal activity.

General 003

Preoperative warming before clean surgery prevents wound infections and can avoid the use of prophylactic antibiotics

D.J. Leaper, A.G. Melling, E.M. Scott and B. Ali

Professorial Unit of Surgery, North Tees General Hospital, Stockton-on-Tees, Cleveland

Aims: Wound infection after clean surgery (the majority being hernias, varicose veins and breast) is underestimated; by using a trained and blinded observer with in depth surveillance, and appropriate definitions or wound scores, an infection rate of up to 15% or more may be found. Equally controversial is the value of prophylactic antibiotics in preventing postoperative wound infections.

Methods: Four hundred and twenty-one patients undergoing clean surgery were randomly assigned to a standard (nonwarmed) group or to local (L) or systemic (S) warming using either a Warm-up device or Bair Hugger (Augustine Medical). All patients were followed up by a blinded observer with a diary system using four wound-scoring systems.

Results: In the standard group there were 19/139 infections (13.7 per cent), 5/138 in the L group (3.6 per cent) and 8/139 in the S group (5.8 per cent; $P < 0.001$). There were no increases in wound complications but the unwarmed patients received more courses of postoperative antibiotics (15.9 per cent) than warmed patients (6.5 per cent; $P = 0.002$).

Conclusions: Warming patients prior to clean surgery reduces the wound infection rate and the indication for postoperative antibiotics and prophylactic antibiotics may not be required for clean wound surgery. Patients undergoing breast surgery have the highest wound infection rates, which may be avoided by preoperative warming to lessen delays waiting for chemotherapy or radiotherapy.

General 004

Systematic review of the quality of randomized controlled trials comparing surgical techniques in the general surgical subspecialties

B. Lovett, W. Sawyer, J. Houghton and I. Taylor

Department of Surgery, Royal Free and University College Hospital Medical School, University College London, 67–73 Riding House Street, London

Aims: To compare the quality of randomized controlled trials (RCTs) comparing two general surgical interventions in each of the surgical subspecialties.

Methods: RCTs published between Jan 1980 and Dec 1999 comparing two surgical interventions were identified from Medline, Embase and the Cochrane Collaboration using the parameters *randomized, controlled trial, and surgery*. Reference lists of identified papers were scanned for other suitable studies. Study methodology was evaluated by two independent observers using a modification of a previously published assessment form. Each paper was assessed for 11 points; aim, control group, power of study, patient selection and randomization, demonstration of baseline equivalence, the definition and unbiased assessment of endpoints, clear description of the operative procedure, adequate follow up and appropriate statistical methods. A paper scored 0 if the criterion was not mentioned, 1 if mentioned but inadequate, or 2 if adequately reported, scoring a maximum of 22 points. Trials scoring <16 were regarded as methodologically unsound. Trials scoring >20 were regarded as excellent.

Results:

Score	≥20	>16 and <20	<16
Breast	3 (11.5%)	11 (42%)	12 (46%)
Upper GI	7 (13%)	24 (44%)	23 (43%)
HPB	13 (23%)	26 (46%)	18 (32%)
Colorectal	5 (13.5%)	15 (40.5%)	17 (46%)
Vascular	5 (22%)	8 (35%)	10 (43%)
Hernia	9 (26%)	11 (31%)	15 (43%)
Other	4 (10%)	12 (31%)	23 (59%)
Total	46 (17%)	108 (40%)	118 (43%)

Conclusions: The methodological quality of RCTs in Hepatobiliary, vascular and hernia surgery was better than the average of all the trials studied.

General 005

The benefits of a hernia service in a district hospital

D M G Bowley, D H Bennett, C Porter and A N. Kingsnorth
Department of Surgery, Derriford Hospital, Plymouth

Aims: To analyse the impact of a dedicated hernia service on the provision of hernia surgery in a large district hospital
Methods: A hernia (HS), initially provided by one consultant, was set up in Derriford Hospital in 1996 to provide a comprehensive service for all aspects of hernia care, including complex abdominal wall reconstructions Since its inception, 1015 patients with unilateral or bilateral inguinal hernias have undergone repair under the HS In addition, 35 complex ventral hernias have been repaired using mesh or the component separation technique of Ramirez
Hospital records were analysed to compare HS patients with patients with inguinal hernias repaired under the general surgical service (GSS) over the same period A random sample of 50 patients in each group was sent a questionnaire to investigate postoperative pain and analgesic requirement, days of wound pain, timing of return to normal activities and patient satisfaction
Results: In the last year analysed, HS (now with an additional 4 surgeons from the directorate) used local anaesthetic (LA) in 90 5 per cent of inguinal hernia compared to 22 4 per cent in the GSS The rate of repair as a day case was 81 per cent for HS and 28 per cent for GSS. Of the HS patients, the wound infection rate was 10/1015 (0 98 per cent), the haematoma/seroma rate was 5/1015 (0.49 per cent) and there have been eight recurrences (0 78 per cent) with a median follow-up of 29 months HS patients required significantly less days of postoperative analgesia and returned to normal activities significantly sooner. Overall satisfaction was not significantly different between the two groups For ventral hernias, most of which were tertiary referrals, the morbidity rate was 15 per cent, with mortality and recurrence rate of zero
Conclusions: A dedicated HS has improved patient outcomes with a significant increase in local anaesthetic repairs and day-case inguinal hernia repair with substantial cost savings Concentration of expertise for ventral hernias offers patients a better opportunity for improved outcome

General 006

Post-vasectomy semen analysis how many and how long?

D.B. Ghosh, C Miller and I A Fraser
Leicester and Warwick Medical School, Coventry

Aims: Immotile sperms are frequently detected in postvasectomy semen samples increasing the number of samples analysed and/thus delaying patient benefits of vasectomy To investigate number of examinations and time required to declare postvasectomy patients infertile and develop guidelines for postvasectomy semen analysis
Methods: A retrospective study of post vasectomy semen analysis 'reports of 496 patients at Walsgrave Hospital between 1995 and 97
Results: One thousand, seven hundred and seventy-one samples were analysed for 496 patients Patients positive for immotile sperms 148/496 at 4 months, 68/496 at 6 months 22/496 at 12 months, 1/496 at 34 months 84 per cent of patients >35 years waited 7 months and required at least four samples before becoming azoospermic 92 per cent of patients of patients <35 years became azoospermic in 5 months following vasectomy
Conclusions: Our study indicates immotile sperms persist longer than generally expected A conventional approach that offers testing at 3 months increases the number of examinations. Our study suggests that patients <35 years should not be called for semen examination until 4 months after vasectomy and patients >35 years after 7 months.

ASGBI: Transplantation 1–6 — Thursday 26 April 2001 11:15–12:15

Transplantation 001

Is gadolinium-enhanced magnetic resonance angiography the new gold standard in screening of living renal transplant donors?

G.J. Morris-Stiff, T. Mittal,[1] A. Wood,[1] R.H. Lord, W.A. Jurewicz and C. Evans[1]

Welsh Transplantation Research Group, University of Wales College of Medicine and [1]Department of Clinical Radiology, University Hospital of Wales, Cardiff, UK

Background: Gadolinium-enhanced magnetic resonance angiography (GaMRA) possesses significant advantages over the current 'gold standard' of vascular investigation, digital subtraction angiography (DSA), as it avoids ionizing radiation, iis non-nephrotoxic and non-invasive. This is particularly important when considering living donor kidney transplantation as these donors are healthy individuals.
Methods: The efficacy of MRA in comparison to DSA in identifying renal artery anatomy in potential living renal transplant donors was assessed in a prospective, blinded study. Images were independently analysed by separate consultants for demonstration of the number of main and accessory renal arteries, and the presence of early arterial branching. The results of both imaging modalities were also correlated with operative findings during organ transplantation whenever possible.
Results: During the period April 1998 to August 2000, 25 consecutive donors were evaluated. The number and position of the main renal arteries identified by both modalities was identical. All seven accessory arteries seen on DSA were visualized by MRA, which also identified an additional artery (sensitivity 100 per cent; specificity 98 per cent, PPV 88 per cent and NPV 100 per cent). Six of seven early branches seen on DSA were also seen on MRA but one branch seen on DSA was not visualised by MRA (sensitivity 86 per cent; specificity 100 per cent, PPV 100 per cent and NPV 98 per cent). The operative findings did not contradict the radiological images.
Conclusions: GaMRA shows comparable efficacy to DSA in the identification of renal artery anatomy, and with a significantly better safety profile. GaMRA should now be regarded as the new investigation of choice for screening of potential living organ donors. Further evaluation is continuing to assess whether it indeed should be considered the 'gold standard' for investigation of all vascular disease.

Transplantation 002

Rapamycin increases the expression of genes responsible for extracellular matrix remodelling compared to neoral in rat allografts

G.J. Murphy, G.R. Bicknell, R.N. Saunders, M.S. Metcalfe and M.L. Nicholson

Division of Transplantation, University Department of Surgery, Leicester General Hospital, Leicester, UK

Aims: Progressive allograft vasculopthy and organ fibrosis remain an important cause of late organ-transplant failure despite improvements in early graft survival with modern immunosuppressive regimens. The aim of this study was to measure the effects of novel immunosuppressive agents on the expression of genes that control extracellular matrix turnover and cell migration in both of these processes.
Methods: Thoracic aortas from F344 rats were transplanted heterotopically into the abdominal aorta of Lewis recipients. F344 to F344 *horacic to abdominal aortic isografts served as controls. Experimental groups received Neoral 5 mg kg^{-1} day^{-1}, rapamycin 0.5 mg kg^{-1} day^{-1} or no treatment. At 4,8,12 and 16 weeks post transplantation six grafts in each group were harvested and analysed histologically. mRNA was extracted from frozen tissue and expression of fibrosis-associated genes was studied by means of quantitative reverse transcriptase-polymerase chain reaction.
Results: Between eight and 16 weeks weeks untreated allografts developed significantly greater intimal thickening compared to isografts (intimal/medial ratio 0.2 ± 0.05 v 0.06 ± 0.07, $P<0.01$) and progressive expansive vascular remodelling (vessel circumference 4223 ± 143 µm v 3709 ± 163, $P<0.05$). Neoral significantly inhibited neointimal hyperplasia (0.08 ± 0.09, $P<0.05$) as well as expansive vascular remodelling (3845 ± 196 µm, $P<0.05$). apamycin significantly inhibited intimal hyperplasia (0.02 ± 0.01) relative to untreated allografts ($P<0.01$) and Neoral ($P<0.05$) but had no effect on expansive vascular remodelling. Levels of gene expression at 8 weeks post-transplant for species important in extracellular matrix remodelling are listed below. Values are expressed as a ratio of the house keeping gene GAPDH.

	Allograft (No Treatment)	Neoral	Rapamycin
MMP 2	1.65 ± 0.18	2.33 ± 0.61†	3.74 ± 1.59†
MMP 9	3.41 ± 0.92	3.40 ± 1.40	6.04 ± 2.05 ±
TIMP 1	1.42 ± 0.43	2.30 ± 0.67 ±	6.07 ± 2.9‡*
TIMP 2	3.33 ± 1.08	4.94 ± 1.18 ±	10.26 ± 4.53†*
Collagen 3	1.39 ± 0.46	2.45 ± 0.62†	5.30 ± 2.79†
TGFβ	2.33 ± 0.78	3.12 ± 0.82	6.88 ± 3.18†*

± = $P<0.05$ *vs.* allograft, † = $P<0.01$ *vs.* allograft, *$P<0.05$ *vs.* Neoral, Mann–Whitney. Mean values ± standard deviation.

Conclusions: These data suggest that Rapamycin inhibits the development of allograft vasculopathy and that this is associated with a significant up-regulation in genes that regulate extracellular remodelling and smooth muscle cell migration.

Transplantation 003

Rapamycin and reduced dose cyclosporin produce effective immunosuppression for *de novo* renal transplant recipients

R.N. Saunders, M.S. Metcalfe, G.J. Murphy, R. Kimber, S.A. White and M.L. Nicholson

University Department of Surgery, Leicester General Hospital, Leicester, UK

Introduction Cyclosporin (CyA) causes both acute and chronic nephrotoxicity and thus attempts are underway to limit CyA exposure in renal transplantation. Rapamycin (Rapa) is a non-nephrotoxic drug with synergistic immuno-suppressive properties when combined with CyA. The aim of this study was to determine the safety and efficacy of a reduced dose CyA/Rapa regimen compared to conventional full dose CyA and FK506 regimens in *de novo* renal transplant recipients.
Methods: Forty-five consecutive cadaveric renal transplant recipients were studied. Fifteen patients initially received CyA 5 or 7 mg kg^{-1} day^{-1} with Rapa 2 mg day^{-1}, 15 received CyA 15 mg kg^{-1} day^{-1} and 15 received FK506 0.2 mg kg^{-1} day^{-1}. All patients were given prednisolone 20 mg kg^{-1} . Full dose CyA was reduced by 2 mg kg^{-1} $week^{-1}$ aiming to achieve trough levels of 300 ng mL^{-1} at 1 month. Reduced dose CyA and FK506 were adjusted to maintain trough levels at 150–200 ng mL^{-1} and 5–15 ng mL^{-1} after 1 month, respectively. Data were analysed on an intention to treat basis.
Results: Patient characteristics, HLA mismatch and ischaemic times were similar in each group. One patient taking full dose CyA and one taking Rapa died. Allograft survival was 14/15 (93 per cent), 11/15 (73.3 per cent) and 14/15 (93 per cent) in each group, respectively. Acute rejection occurred in 4/15 (27 per cent) Rapa, 4/15 (27 per cent) full dose CyA and 5/15 (33 per cent) full dose FK506 patients. Delayed graft function was seen in 2 patients in both full dose regimens and 3 of those taking Rapa. After 3 months follow-up, mean serum creatinine (±SD) was 149 (64) *vs.* 179 (89) *vs.* 141 (61) µmol L^{-1} and mean (±SD) estimated GFR was 67.9 (26.7) *vs.* 62.3 (33.2) *vs.* 64.3 (21.8) mL min^{-1} for each group, respectively. Rapa caused hypertriglyceridaemia that was persistent at 3 months (3.24 (1.49) *vs.* 1.83 (0.60) *vs.* 1.91 (0,85) mmol mL^{-1}, $P<0.01$). There were no significant differences in serum cholesterol between groups but 7/15 Rapa patients were started on HMG CoA reductase inhibitors over this period compared to 2/15 and 1/15 in the full dose CyA and FK506 groups ($P<0.05$). Rapa did not cause clinically relevant haematological abnormalities.
Conclusion The use of a combination of Rapa and reduced dose CyA in denovo renal transplant recipients is safe and effective, yielding results comparable to conventional immunosuppressive regimens. Although hyperlipidaemia was not dramatic a significant proportion of the Rapa patients were taking lipid-lowering medication.

Transplantation 004

Normothermic preservation of non-heart-beating donor livers

C. J. Imber, S.D. St. Peter, I. Lopez, D. Piggott, S. Saville, S. Fuggle and P.J. Friend

Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK

Aims: We would like to introduce a novel method of liver preservation applied to the non-heart-beating donor using continuous normothermic, sanguinous perfusion in the porcine model. This method will allow for greater recovery of function than the traditional method of cold storage provides

Methods: Pigs weighing 30–50 kg underwent laparotomy and were given 1 hour of circulatory arrest prior to flushing, harvesting, and preserving the liver for 24 h by either cold storage in UW solution or normothermic, sanguinous perfusion on an extracorporeal circuit After the preservation period, both groups are then placed on the circuit with sanguinous perfusion for 24 h to assess the livers for function and adequacy of preservation

Results Livers preserved using normothermic preservation demonstrate earlier recovery of function, and superior bile production, glucose utilisation, and pH control The normothermically preserved livers also show less preservation injury by histology and measured markers of ischaemic–reperfusion injury

Conclusions: Normothermically perfused organs as a method of preservation demonstrate superior recovery of function and preservation compared to the cold stored organs in the non-heart-beating donor Normothermic, extracorporeal perfusion may allow for assessment of viability, extended preservation, and the use of livers from non-heart-beating donors.

Transplantation 005

A new and improved solution for liver preservation

I Ahmed, M S Attia, N Ahmad, C L Corps, D J Potts and J P A Lodge

St James University Hospital Leeds, and School of Biomedical Sciences, University of Leeds

Aims: Further developments in preservation are required to improve organ quality and extend functional lifetime We have compared PBSL, a newly developed phosphate-buffered sucrose based solution with UW, Celsior, HTK, and HL solutions in an isolated perfused rat liver model

Methods: All the experiments were carried out under a Home Office licence and according to normal guidelines of animal care Rats were anaesthetized, the bile duct cannulated, and liver flushed with cold PBSL, UW, Celsior, HTK or HL via the aorta and portal vein to escape from a cut inferior vena cava After flush the liver was removed and stored in 60 mL of preservation solution at less than 4°C for 24 h The liver was re-perfused at 37°C at a rate of 15 mL min^{-1} and the following observations of the liver function were made

Results:

PBSL	UW ($n=18$)	Celsior ($n=12$)	HTK ($n=6$)	HL ($n=5$)	($n=6$)
Bile flow ($\mu L min^{-1} g^{-1}$)	78 94±3 32	62 37±3 57*	68 62±2 72	69 05±2 84	71 22±1 4
O_2 Consumption ($\mu mol min^{-1} g^{-1}$)	0 67±0 03	0 71±0 04	0 54±0 05	0 48±0 41	0 482±0 96
LDH release (UL^{-1})	411±22 38	612±10 24*	618±25 56*	668±48 19*	566±22 27*
ALT release (UL^{-1})	42 88±4 03	62 11±6 6*	86 84±3 89*	63 12±18 5*	56 62±4 75
AST release (UL^{-1})	39 82±4 24	68 22±7 85*	88 53±9 15*	85 43±28 1*	44 49±6 56
Portal pressure (kPa)	3 2±0 07	3 1±0 05	3 25±1 1	3 1±0 05	3 2±0 8
Weight change (%)					
After storage	−2 94±0 41	−3 55±0 47	1 8±0 74*	1 37±0 56*	−1 98±0 81
After reperfusion	−0 09±1 43	4 49±0 42*	3 91±1 59*	2 26±0 92	3 4±1 39*

Mean ± SEM, * $P<0\ 05$ (one way analysis of variance)

Conclusions: PBSL provides better preservation than other solutions in the isolated perfused rat liver model This solution would be expected to provide better quality preservation in clinical use

Transplantation 006

Management of biliary complications following orthotopic liver transplantation

G C Oniscu, S Thethy, H Pleass, J L R F Forsythe, K K Madhavan, M Akyol and O J Garden

Scottish Liver Transplant Unit, The Royal Infirmary of Edinburgh

Aims: Biliary complications following OLT pose a significant problem and often require serial interventions before complete resolution Our aim was to assess the management of biliary complications and their success within a single liver transplant unit.

Methods: Data regarding biliary complications in liver Tx recipients was prospectively recorded on a computerised database. We analysed retrospectively the incidence and the type of biliary complication, the management sequence and its success rate Success was defined as no further need for biliary intervention Statistical analysis was performed with the SPSS program version 9.0 using χ^2 and Fisher's exact test where appropriate

Results: Three hundred and one consecutive liver transplants have been performed since November 1992 298 were analysed (3 deaths on table) 47 grafts developed biliary complications giving an overall incidence of 15 8 per cent The correlation between the modality of biliary reconstruction and the type and incidence of biliary complications is illustrated in the table below There was a higher incidence of complications in the hepatico-jejunostomy group (24 per cent) compared with the duct-to-duct technique (12 per cent) ($P=0\ 035$, χ^2).

	Duct-to-duct	Duct-to-duct with T-tube	Hepatico-jejunostomy	Total
Number performed	200	56	42	298
Number of biliary complications (%)	23 (12)	14(25)	10 (24)	47 (15 8)
Anastomotic leaks (%)	10 (5)	4 (7)	6 (14)	20 (6 7)
Anastomotic strictures (%)	14 (7)	9 (17)	2 (5)	25 (8 3)
Other complications (%)	1 (1)	7 (12 5)	2 (5)	10 (3 3)

All 20 anastomotic leaks occurred within 75 days of transplant. 15 (75 per cent) were initially managed conservatively with a success rate of 73 per cent (11 cases) Endoscopic stent insertion and radiological techniques were successful in three out of seven cases (42 per cent), while surgery resolved all four cases (100 per cent) where it was employed Out of the 20 cases with initial leaks, seven (35 per cent) developed a subsequent stricture at a median interval of 164 days (range 49–709 days) There were 25 strictures, with a bi-modal distribution (14 cases <6 months, 11 cases >6 months) 22 cases (88 per cent) were initially managed using a nonsurgical technique, with a success rate of 31 8 per cent (seven cases), while 12 cases required further surgery before complete resolution of the complication Eight (73 per cent) of the anastomotic strictures occurring after 180 days post-transplant required surgical management compared to 4 (28 per cent) that occurred before 180 days ($P=0\ 02$, χ^2)

Conclusions: Biliary leaks and early strictures can be successfully managed by a combination of conservative, endoscopic and radiological means Late strictures appear to be best treated by primary surgical repair

ASGBI: Paediatric 1–4 Thursday 26 April 2001 14:00–15:20

Paediatric 001

General paediatric surgery – who and where?

A. O'Donovan, H. Varadaraj, H. Flood, P. Delaney, J. Drumm and P.A. Grace

Departments of General Surgery and Urology, Mid-western Regional Hospital, Dooradoyle, Limerick, Ireland

Aims: General surgeons in Great Britain and Ireland are providing a general paediatric surgical service in regions without a specialist paediatric surgery unit. Our aim was to review the provision of this service in the mid-western health region in the Republic of Ireland and to predict the future of general paediatric surgery in the region.
Methods: Over the period January 1995 to January 2000 the general paediatric surgical workload in the Mid-western Regional Hospital was audited. Using operative logbooks, patient charts and the HIPE system, the operation performed, the operator, the nature of the operation and the mortality and morbidity were recorded. Numbers of patients transferred to a specialist paediatric surgical unit and the reason for transfer were elicited. Figures were obtained for the yearly birth rate to predict future trends.
Results: Two thousand, three hundred and fifty-three paediatric operations were performed. 813 other paediatric surgical patients were treated conservatively. Over the period there was an increase in the percentage of day cases (55 per cent to 70 per cent) and the percentage with a consultant as the main operator (40 per cent to 67 per cent). There was no mortality and less than 1 per cent morbidity. Only 57 patients were transferred to a specialist unit. During our study period the birth rate increased by over 700 births per year (3301–4024).
Conclusions: At present general paediatric surgery is adequately provided for the region by appropriately trained general surgeons, but with a decreasing number of general surgeons receiving the appropriate six months paediatric surgery we are facing a crisis in the provision of this service. Increased numbers of specialist paediatric surgeons or a change in general surgical training is required.

Paediatric 002

Splenectomy after paediatric trauma: could more spleens be saved?

P. Godbole and M.D. Stringer

Department of Paediatric Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Aims: Guidelines for the emergency management of paediatric splenic trauma became widely available in 1993. A regional survey was undertaken to assess the application of Advanced Paediatric/Trauma Life Support guidelines to children who had undergone splenectomy after trauma.
Methods: All children who had undergone splenectomy for a ruptured spleen at eight district hospitals and two teaching hospitals in our region between January 1994 and January 1999 were identified from histopathology departmental records. With appropriate permission their case notes were reviewed.
Results: Eleven children (nine males) were identified, all from district hospitals, with a median age at presentation of 11.8 (6.7–16.8) years. All presented within 6 h of blunt abdominal trauma. Median systolic blood pressure, pulse rate, haemoglobin concentration and Injury Severity Score (ISS) on admission were 115 (80–140) mmHg, 108 (84–150) per minute, 12.1 (10.7–12.8) g dL^{-1} and 17 (17–29), respectively. Three children had additional injuries (fractured clavicle, tension pneumothorax, and a minor renal laceration). On admission, three children received an intravenous fluid bolus of 20 mL kg^{-1} and the remainder received only maintenance fluid requirements or less. Five children were investigated by ultrasound imaging, one by double contrast CT scan, and three by laparoscopy. Two children had no imaging studies prior to laparotomy. Laparotomy was performed by a consultant surgeon in seven and by a specialist registrar in four. Ten children underwent total splenectomy and one child had a partial splenectomy. Median hospital stay was 7 (5–10) days. The child with an ISS of 29 developed a persistent pancreatic fistula which subsequently required a distal pancreatectomy. All children received Pneumovax and penicillin prophylaxis.
Conclusions: None of these cases fulfilled the recommended criteria for laparotomy in children with blunt abdominal trauma. Splenectomy may have been avoidable with more appropriate management.

Paediatric 003

Hospital re-admission in children with nonspecific abdominal pain

P.A. Barker, R.S. Jutley and G.G. Youngson

University of Aberdeen, UK

Aims: To evaluate the outcome of children with nonspecific abdominal pain (NSAP) who were subsequently re-admitted to hospital, with a further episode, within a period of 30 days. The contribution of active observation to the initial and subsequent admission was evaluated and the diagnostic process reviewed.
Methods: The cohort comprised all children with a discharge diagnosis of NSAP admitted to Royal Aberdeen Children's Hospital between 1/1/1990 and 31/12/1999. A measure was made of the investigations employed and an arbitrary score produced reflecting the intensity and degree of the diagnostic process. Clinical outcome was related to the investigation score and revision of diagnoses was identified.
Results: One thousand, two hundred and thirty-eight children (675 males, 563 females) were admitted with NSAP. 46 (22 males and 24 females; age range 4–14 years) were re-admitted with further abdominal pain within 30 days. The total number of re-admission events was 53. In 19 children the subsequent diagnosis was revised. 10 of the 46 children underwent operation. In 31 cases investigations on re-admission were more detailed and invasive but produced no change in diagnosis in 18.
Conclusions: Most children will undergo more invasive and detailed investigations on re-admission, however, the majority will continue to be managed conservatively. This study endorses the continued use of active observation in the management of abdominal pain in children, and recognises that even intense investigation often fails to contribute to a more specific diagnosis.

Paediatric 004

The use of GTN for the treatment of chronic anal fissures in children

J. Simpson,[1] J.N. Lund,[1] R.J. Thompson,[2] L. Kapila[2] and J.H. Scholefield[1]

[1]*Departments of Surgery and* [2]*Paediatric Surgery, University Hospital, Nottingham, UK*

Aims: 0.2 per cent topical glyceryl trinitrate (GTN) ointment heals up to two-thirds of chronic anal fissures in adults although many patients experience troublesome headaches. This double blind randomized pilot study assessed the efficacy and side-effects of 0.1 and 0.05 per cent GTN ointment in treatment of chronic anal fissures in children.
Methods: Fifteen consecutive children with chronic anal fissures were randomised to receive either 0.05 or 0.1 per cent GTN ointment applied topically twice daily for eight weeks. Clinical review was undertaken at weeks 4 and 8 and questions relating to bowel function and the incidence of headache were asked.
Results: The median age of the 15 (eight male) patients was 6 years (range 3–13). There were five anterior and 10 posterior fissures. The median duration of symptoms was 9 (3–30) months. 13/15 (86.7 per cent) patients were taking laxatives at the time of referral. Fissure healing was complete at 8 weeks in all seven patients who received 0.05 per cent and in 5/8 (62.5 per cent) patients using the 0.1 per cent ointment (Fisher's exact test, not significant). One patient from each arm experienced headaches during the first week of the trial that resolved without treatment and did not affect compliance. There were no other side-effects.
Conclusions: Topical glyceryl trinitrate ointment is effective in healing chronic anal fissures in children. Healing rates and side-effect profile are comparable when either 0.05 or 0.1 per cent ointment is used.

ASGBI: Trauma/General 1–5

Thursday 26 April 2001 14:20–15:10

Trauma/General 001

Non-orthopaedic injuries associated with spinal trauma; an eight-year review from the National Spinal Injuries Unit of Ireland

I. Norton, K Synott, M. Walsh and D McCormack
Spinal Injuries Unit, Mater Misericordiae Hospital, Dublin, Ireland

Aims: Spinal injuries are frequently the result of major trauma and are often just a part of a patient's overall injuries. These related injuries are often more life-threatening to the patient, provide a potential danger in transfer and place a heavy burden on the receiving hospitals' resources Our aim was to examine the incidence and treatment required for patients in our unit with related non-orthopaedic injuries.
Methods: We reviewed the records of 1337 patients with 1490 spinal injuries treated between January 1993 and June 2000.
Results: Four hundred and forty-five (33.3 per cent) patients had other injuries, this represented 29 per cent of cervical, 42 per cent of dorsal, and 33 per cent of lumbar fractures. The injuries associated with fractures in each spinal region are shown in the table (per cent of all fractures in that region in brackets).

Injury	Cervical (Total 735)	Dorsal (Total 329)	Lumbar (Total 426)	Procedures (Total)
Head	63 (8 6%)	27 (8 2%)	19 (4 4%)	4 Neurosurgical proc
Chest	49 (6 6%)	85 (26%)	45 (10 6%)	65 chest drains, 2 ops
GI	10 (1 4%)	10 (3%)	6 (1 4%)	22 DPLs, 17 ops
GU	0	5 (1 5%)	5 (1 2%)	see above
Skin/Plastics	83 (11 3%)	37 (11 2%)	25 (5 9%)	35 ops
Max-Fax/Dental	21 (2 9%)	10 (3%)	10 (2 3%)	12 ops

Conclusions: We have highlighted the frequent incidence of serious trauma associated with spinal injury and have shown the type of injuries to seek at various spinal injury levels We will also give a clear indication of the workload that accompanies spinal injuries in a large tertiary unit.

Trauma/General 002

Emergency admissions for head injury in the elderly

D Lawes
King George Hospital, Barley Lane, Ilford, Essex, UK

Aims: To evaluate the outcome in elderly patients admitted under the care of the General Surgeons following head injury.
Methods: A retrospective review of emergency admissions, following head injury was performed. Patients included were >75-year-old at presentation and admitted under the care of a general surgical consultant. The study period ran from 1st July 1996–31st June 1998. The reason for admission, length of hospital stays and the method of discharge were recorded.
Results: Fifty-five patients with a mean age of 83 8 years (range 75–97) were reviewed. The average length of stay was 6.65 days (range 1–47) Four patients had a Glasgow Coma Score (GCS) of <13, all had intracranial injuries but only one was considered fit for neurosurgical intervention. 51 patients had a GCS>13, 25 (49 per cent) were admitted for social reasons, 10 (19.6 per cent) for observation, nine (17 6 per cent) for confusion and seven (13 7 per cent) due to other injuries. Patients occupied surgical beds for a total of 366 days. 160 days were spent awaiting transfer to another hospital, 157 days waiting for social services, 24 days waiting for a terminal outcome and 12 days for unspecified reasons
Conclusions: Elderly patients with head injuries rarely require neurosurgical intervention Complex social requirements and extensive medical conditions often give rise to prolonged hospital admissions Physicians specialising in elderly care medicine might manage these patients more appropriately.

Trauma/General 003

Penetrating neck injuries in a major urban trauma centre

D M G. Bowley, P Barker, G Hersman, J. Goosen and K D Boffard
Johannesburg Hospital Trauma Unit, Johannesburg, South Africa

Aims: The management of penetrating injuries to the neck has evolved in recent years. A review of penetrating injuries to the neck over a 5-year period at a major urban trauma centre was undertaken to consider the experience gained in the management of these complex injuries.
Methods: A retrospective review was made of all patients undergoing exploration for gunshot wounds or stabs to the neck between Jan 1994 and Dec 1998
Results: A total of 346 patients underwent exploration 312 patients were male (91 per cent) and the age range was 12–69 years (mean 24 years), of whom 9 per cent died in hospital. There has been a major increase in penetrating neck injuries since 1994 and gunshot wounds are now more common than stabbings
Conclusions: A policy of mandatory exploration of neck wounds has been found to be no longer sustainable in the face of increasing caseload and scarce resources. A policy of selective conservatism is practised in the Trauma Unit and guidelines to manage these potentially lethal injuries are presented.

Trauma/General 004

Gunshot wounds: training and service implications.

A Cowey, P. Mitchell, J Gregory, I. Maclennan and R.C Pearson
Manchester Royal Infirmary, Oxford Rd, Manchester M13 9WL, UK

Aims: Violence involving the use of firearms has increased in the UK over the past decade This study assesses the implications of such injuries for service provision and training by reviewing the experience at one inner city hospital
Methods: Accident and Emergency (A & E) triage data were searched for patients presenting with gunshot wounds (GSW) over a 54-month period Case notes were reviewed and patterns of care established The resources required for clinical management were ascertained, and the financial consequences determined at contemporary full cost
Results: There were 187 attendances with 247 wounds Mean age was 21 years (range 8–63) 69 per cent attended out of normal working hours. 97 patients were admitted to one hospital, 83 of whom required surgery. 10 patients were transferred to other hospitals. Of the remaining 80, 4 died in A & E, the rest were either airgun wounds or relatively simple higher calibre injuries. A wide range of surgical specialities was involved (limb injury 80, thoraco-abdominal and vascular 35, head and neck eight, orbit four), and combinations of injuries transgressed speciality and subspecialty boundaries The total cost of patient care was over £1/4 million, 98 per cent of which was in patient costs (mean in patient cost £2700, range £140–£40 k)
Conclusions: GSW present a heavy demand on the clinical and financial resources of the receiving hospital, and surgeons responsible for unselected acute admissions in 'General Surgery' should be capable of dealing with theses indiscriminate injuries Current training and service trends towards increasing subspecialization may militate against them achieving or retaining this capability.

Trauma/General 005

Primary repair of penetrating colonic wounds

D M G Bowley C McNab, P. Barker, J Goosen and K.D. Boffard
Johannesburg Hospital Trauma Unit, Johannesburg, South Africa

Aims: The management of penetrating colon injuries has evolved over recent years with increasing confidence in the role of primary repair A prospective study was undertaken to analyse the outcome of universal primary repair in unselected patients in a major urban trauma centre
Patients and methods: This was a prospective study of patients with colon injury due to penetrating trauma between March and October 2000. Demographic data, wounding agent, time from wounding to surgery, site of colonic wound, degree of faecal contamination, associated injury and presence or absence of hypotension were documented Outcome measures used were mortality, rates of anastomotic leakage, intra-abdominal and wound sepsis, fascial dehiscence and pulmonic complications Total hospital stay was recorded
Results: Patients who died from refractory hypovolaemic shock within the first 48 h were excluded Thirty-four patients fulfilled the criteria for analysis. There were 32 males and ages ranged between 17 and 17 years (median 29 years). There were only two stab wounds, the rest being gunshots Median time from wounding to surgery was 2 h (range 45 mins to 48 h). Overall, 26 patients (76 per cent) were managed by primary anastomosis and seven (20 per cent) by resection and primary anastomosis One patient had a damage control operation with anastomosis at relook surgery All patients who lived beyond 48 h survived. There were two anastomotic leaks (6 per cent), intra-abdominal sepsis without leakage in 3 per cent, abdominal dehiscence in 9 per cent, wound sepsis occurred in six patients (17 5 per cent) and severe pulmonary complications in two patients (6 per cent)
Conclusions: In view of our findings, we believe that primary repair following penetrating trauma can be achieved with acceptable morbidity, irrespective of associated risk factors Faecal diversion is known not to protect from colon-related complications and as colostomy also mandates subsequent operation and reduces quality of life, its use should be abandoned

ASGBI: Six of the Best Breast — Thursday 26 April 2001 14:30–15:30

Breast 001

Long-term results of randomized studies of axillary clearance *versus* nontargeted axillary sampling

P.A. Lambah, J.M. Dixon, R.J. Prescott, W. Jack, A.P.M. Forrest and U. Chetty

Edinburgh Breast Unit, Western General Hospital, Edinburgh, UK

Aims: To compare statistics for patient survival and axillary recurrence in 857 women treated by either axillary node clearance or axillary node sampling on the Edinburgh Breast Unit between 1980 and 1995.

Methods: Eight hundred and fifty-five women with operable T_1-T_3, N_0 N_1, M_0 breast cancer were enrolled in two consecutive studies of mastectomy (Mx), $n = 401$ or wide local excision (WLE) $n = 454$ and were randomized to four-node sampling (NS) or clearance (NCI). All patients with involved nodes on NS had axillary radiotherapy (XRT). Systemic therapy was based on node status and identical in both randomized groups. Mean follow-up was 4429 days for Mx, 2538 days for WLE and 3434 days for the combined group.

Results: In the Mx and WLE groups there was no significant difference in axillary recurrence within node positive (+) or node negative (–) groups whether patients had NS or NCI. A combined updated analysis to 1999 by treatment received showed significant differences (Table).

Combined group	*n*	Axillary recurrence 5y	10y	15y	*P*-value	Survival 5y	10y	15y	*P*-value
NS–	283	3.7	7.2	7.2	0.023	89.8	83.9	69.5	0.36
NCI–	260	2.0	2.0	2.0	88.8	77.4	66.9		
NS+	148	7.3	10.9	0.036	75.3	58.1	49.2	0.57	
NCI+	164	3.1	6.5	6.5	76.8				

y, years.

Conclusions: Axillary clearance produces significantly better control of the involved axilla than NS followed by XRT. Non-targeted four-node axillary sampling is accurate and safe.

Breast 002

Intra-operative frozen section reliably predicts sentinel node status in patients with primary breast cancer

M.E. MacLean, J. Going, M.M. Flett, C.R. Wilson and T.G. Cooke

University Departments of Surgery and Pathology, Glasgow Royal Infirmary

Aims: Studies have shown that routine histology of the sentinel node reliably predicts nodal status of the axilla, however, this does not allow for an intraoperative decision on whether axillary node clearance is required. We have performed intraoperative frozen section analysis on sentinel nodes to see if this can be used to predict reliably the necessity for axillary node clearance.

Methods: Of 206 sentinel nodes harvested from 145 patients, 91 nodes from 85 patients underwent frozen section analysis. A formal axillary node clearance was then completed. All harvested nodes including the sentinel node were then analysed by routine histology.

Results: Of the 85 patients 23 had a positive frozen section. Subsequently 1/23 patients was found to be negative by paraffin histology. 62 of the 85 patients had a negative frozen section however, five of these patients had positive paraffin histology. These results therefore represent a specificity of 98.3 per cent (PPV 96.4 per cent) and sensitivity of 82.1 per cent (NPV 92.1 per cent).

Conclusions: Intra-operative frozen section reliably predicts the status of positive sentinel nodes and based on these data, 6 per cent of patients would have required a second stage axillary node clearance and 1 per cent of patients would have had an unnecessary procedure due to a false-positive result. We conclude that intraoperative frozen section of the sentinel node can be used clinically to decide whether axillary node clearance is indicated and in our series, 67 per cent of patients would have avoided this.

Breast 003

Positive cavity biopsy does not predict early local recurrence in patients with breast cancer treated with breast conserving surgery and post-operative radiotherapy

P. Sinha, S. Thrush, S. Bendall and T. Bates

The Breast Unit, The William Harvey Hospital, Ashford, Kent TN24 OLZ, UK

Aims: To determine whether a positive cavity or margin biopsy predicts early local recurrence in patients with invasive breast cancer treated by breast conserving surgery. To further determine whether post-operative radiotherapy (RT) is adequate treatment in patients with positive margins without further surgery.

Methods: Patients with invasive breast cancer treated by breast conserving surgery who had biopsies of the residual cavity between January 1986 and October 1999 were reviewed. The outcome in terms of local recurrence is compared in those patients with a positive cavity biopsy and/or an involved resection margin (positive margin) *versus* those with a clear margin. Those patients with a positive margin who received RT without further surgery are compared with those with clear margins who received RT. Local recurrence rates were compared by Kaplan–Meier analysis and the log-rank test.

Results: Of 469 patients treated by conservative surgery 127 (27 per cent) had positive margins with either invasive or *in situ* disease in the ratio 50:50. There were 342 patients with clear resection margins but the local recurrence rate was 5.5 per cent in both groups at a mean follow-up of 68 months. Of the 127 patients with positive margins, 53 were treated by mastectomy and 13 by re-excision to clear margins + RT. However, in the early part of the study 46 patients with positive margins were treated by RT alone. 15 elderly patients were treated by tamoxifen alone. Of the 342 patients with clear cavity biopsies and margins, 198 were treated by RT. There were 3/46 (6.5 per cent) local recurrences in patients with positive margins *versus* 6/198 (3 per cent) in those with clear margins but due to the longer follow-up of the positive margin group (mean 72 months *versus* 66 months) the difference in recurrence free survival between the two groups was not significant (log rank $P = 0.29$).

Conclusions: Contrary to expectation, positive biopsies of the residual cavity and/or the resection margin after conservative surgery for invasive breast cancer, failed to predict subsequent local recurrence. Furthermore, those patients with positive margins and presumed residual disease who were treated by RT without further surgery did not have significantly increased local recurrence.

Breast 004

Extent of ductal carcinoma *in situ* within and surrounding invasive primary breast carcinoma: association with other prognostic factors, survival and recurrence

R.S. Rampaul, N. Crombie, S.E. Pinder, J. Bell, D.M. Macmillan, J.F.R. Robertson, R.W. Blamey and I.O. Ellis

Nottingham City Hospital, Nottingham, UK

Aims: To evaluate the pathological and morphological features of DCIS within and surrounding invasive ductal carcinoma, and investigate its relationship to clinical outcome and established prognostic variables.

Methods: One hundred and seven patients (107) with primary operable invasive breast carcinoma and associated DCIS treated by simple or subcutaneous mastectomy or wide local excision with radiotherapy were assessed. Cases of pure DCIS and those with insufficient tumour available for examination were excluded. The most representative haematoxylin and eosin-stained sections of the remaining 91 cases which included the invasive tumour and surrounding normal tissue were selected and examined at 100 × magnification using a 45-point 2 mm grid graticule. The entire section was assessed and the cell under each point of the graticule was classed as either (a) normal; (b) DCIS surrounded by normal tissue; (c) invasive tumour; or (d) DCIS surrounded by invasive malignancy. The volume ratio of DCIS in the normal $[(b)/(a+b)]$ and invasive tissue $[(d)/(c+d)]$ was then calculated.

Results: The DCIS volume within invasive tumour was not associated with outcome, however, the DCIS volume within adjacent normal tissue was associated with disease-free interval ($P = 0.048$), local recurrence ($P = 0.020$), regional recurrence ($P = 0.0543$), the occurrence of distant metastases ($P = 0.019$), death from breast cancer ($P = 0.036$) and overall survival ($P = 0.036$). Volume ratios of DCIS in normal and invasive tissue were not related to known prognostic factors including lymph node stage, grade, tumour size, vascular invasion or patient age.

Conclusions: In patients with an invasive cancer the volume of DCIS in normal surrounding tissue is a significant prognostic factor. We presume the prognostic significance is due to an association with an as yet unidentified component of the invasive cancer

Breast 005

Comparison of margin status with van Nuys index to predict recurrence of ductal carcinoma *in situ* after breast conserving surgery

G P Boland, K.C. Chan, W F. Knox and N J. Bundred

Department of Surgery & Pathology, University Hospital of South Manchester, UK

Aims: Selection of patients for radiotherapy after breast conserving surgery (BCS) for unifocal ductal carcinoma *in situ* (DCIS) is determined by recurrence risk The van Nuys prognostic index (VNPI combining tumour grade, size and resection margin width) has been claimed in the USA to predict recurrence, therefore we aimed to validate this and compare VNPI with a simpler measure of margin clearance to predict recurrence after BCS for DCIS

Methods: Clinico-pathological data for 228 patients treated with BCS for DCIS were compared for risk factor of recurrence Median age of patients was 56 years and the median follow up was 48 months Patients were placed in three groups based on VNPI score. Data were analysed for proximity of margins (close <1 mm or not) and by Van Nuys subgroups.

Results: There were 36 ipsilateral recurrences (27 DCIS and nine invasive cancers).

		Recurrence		
Variable	*n*	No	Per cent	*P*-value
VNPI Groups				
3 & 4	33	0	0	
5	42	3	7.1	0.001
6, 7 & 8	152	33	21.7	
Proximity of margin				
Close (<1 mm)	73	27	36.9	<0.001
Not close (≥1 mm)	154	9	5.8	
Grade Van Nuys				
I or II No necrosis (1)	53	3	5.6	
I or II Necrosis(2)	31	5	16.1	0.048
III (3)	144	28	19.4	

Conclusions: Logistical regression shows that close resection margins (<1 mm) alone is a better predictor than the VNPI for DCIS recurrence.

Breast 006

Surgery for early breast cancer improves survival in the elderly: result of a randomized trial of tamoxifen alone *versus* surgery plus tamoxifen

T. Bates,[1] M. Fennessy,[2] J Latteser,[2] K MacRae,[3] D.L. Riley,[2]
J. Houghton[2] and M Baum[2]

CRC Breast Cancer Trials Group, [1]William Harvey Hospital, Ashford, [2]2CRC and UCL Cancer Trials Centre, and [3]Charing Cross Hospital, London, UK

Aims: Breast cancer has been considered a more indolent disease in the elderly compared to younger women. The aim of this trial was to test the hypothesis that tamoxifen alone would provide adequate control of breast cancer over the normal expectation of life of an elderly woman, thereby sparing them surgery

Methods: Patients with operable invasive breast cancer aged over 70 were randomized to either tamoxifen alone, 40 mg daily, or surgery plus the same dose of tamoxifen As the tumour was still *in situ* in half the patients, the first change of management (COM) was taken to signal primary treatment failure in place of recurrence-free interval. Overall and breast cancer mortality was compared in the two groups

Results: Between 1984 and 1992, 455 patients with operable disease were randomized into the trial. This analysis is based on a median follow-up of 12.3 years. The COM-free interval was significantly shorter in the tamoxifen-alone group (hazard ratio (HR) = 2.80 (95 per cent confidence interval (CI) = 2.09–3.74)) as was the progression-free interval (HR = 4.42(95 per centCI = 3.33–5.87)) For surgery-plus-tamoxifen patients the most frequent intervention was hormonal therapy (51 per cent) whereas for tamoxifen-alone patients it was surgery (64 per cent) The greater hazard ratio for progression-free interval compared to COM-free interval is due to a delay in changing management once patients in the tamoxifen-alone group had evidence of progression Overall mortality and mortality from breast cancer were significantly increased in the tamoxifen-alone group compared to the surgery-plus-tamoxifen group, HR = 1.3 (95 per cent CI = 1.05–1.61) and HR = 1.75 (95 per cent CI = 1.18–2.59), respectively. Stratification of overall mortality by age and tumour size suggested that patients aged 70–72 or with T3 tumours had an increased mortality when treated with tamoxifen alone compared to surgery-plus-tamoxifen, HR = 2.00 (95 per cent CI = 1.18–3.39) and HR = 2.51 (95 per cent CI = 1.21–5.20), respectively.

Conclusions: This trial has shown that the omission of primary surgery in elderly patients with operable breast cancer who were fit for the procedure has resulted in earlier therapeutic intervention and an increased mortality.

ASGBI: Six of the Best Colorectal — Thursday 26 April 2001 16:00–17:00

Colorectal 001

Meeting the two-week target for colorectal cancer in Somerset: a prospective study

R.J. Davies,[1] R. Welbourn,[2] C. Collins,[2] R. Kennedy[1] and C. Royle[1]

Department of General Surgery, [1]*Yeovil District Hospital and Taunton and* [2]*Somerset Hospital, Somerset*

Aims: This prospective study assesses the introduction of a fast-track referral system for patients with suspected colorectal cancer referred to two District General Hospitals in Somerset.

Methods: Following a series of educational presentations to local general practitioners, the referral system was initiated in Yeovil District Hospital and Taunton and Somerset Hospital on 1 November 1999. Six screening criteria were used to select high-risk patients and data on these patients were recorded prospectively over an initial 6-month period (1 November 1999 to 30 April 2000). Patients with proven colorectal cancer diagnosed between 1 November 1998 and 30 April 1999 have been identified for comparison.

Results: Four hundred and thirty-three fast-track referrals were received, with 303 patients (70 per cent) seen within 2 weeks. In total, there were 158 new cases of colorectal cancer (111 elective, 47 emergency). 59 of these patients were diagnosed from fast-track referrals (53 per cent of total elective cases). Median time to diagnosis in the fast-track group was significantly less than for the non-fast-track elective cases (11 *versus* 32.5 days, $P<0.001$). Median time to diagnosis was significantly less for all elective cases compared with those presenting 1 year earlier (17 *versus* 38.5 days, $P<0.001$). 75 per cent of fast-track patients were diagnosed within 2 weeks, compared with 17 per cent of non-fast-track elective patients ($P<0.001$). The proportion of emergency admissions was reduced from 40 per cent to 30 per cent ($P=0.07$) following the introduction of this service.

Conclusions: A fast-track system for suspected colorectal cancer has led to a significant reduction in the time to diagnosis, with the majority of cases diagnosed within 2 weeks.

Colorectal 002

Supervised rectal resection for cancer by specialist surgical registrars is safe

M. Tytherleigh, J. Wheeler, M. Birks and R. Farouk

Royal Berkshire Hospital, Reading, UK

Aims: To assess morbidity, mortality and cancer related outcomes after supervised rectal resection for cancer by surgical specialist registrars (SPR). This was compared with consultant results (CONS).

Patients and methods: The case notes of 197 consecutive patients (113 male; median age 64 years 24–90) who underwent elective resection of their rectal cancer (154 anterior resections; 43 abdomino-perineal resections) were reviewed. The modified Dukes stages were A in 28 patients (14 per cent), B in 47 (24 per cent), C in 92 (47 per cent), and D in 30 (15 per cent).

Results: Sixty-one patients (33 males) of median age 62 years (range, 38–82) underwent supervised resection (52 anterior resections; eight abdomino-perineal resections) by a SPR. Of these patients, seven (11 per cent) were modified Dukes stage A, 13 (22 per cent) stage B, 32 (53 per cent) stage C and eight (14 per cent) stage D.

Postoperative morbidity (SPR 32 per cent *versus* CONS 41 per cent; overall 38 per cent; χ^2 $P=$not significant) and mortality (SPR 2 per cent *versus* CONS 5 per cent; overall 4 per cent; χ^2 $P=$not significant) were comparable with consultant outcomes. Local recurrence rates (SPR 9 per cent *versus* CONS 11 per cent; overall 11 per cent; χ^2 $P=$not significant) and cancer specific survival (SPR 77 per cent *versus* CONS 82 per cent; overall 80 per cent) were also comparable after a median follow-up of 36 months (range, 12–68).

Conclusions: Operative and cancer-related outcomes are not compromised by supervised SPR resections of rectal cancer.

Colorectal 003

Epidural analgesia increases post-operative infections following anterior resection

K.L.R. Grace,[1] P. Durdey,[1] T. Gould[2] and M.G. Thomas[1]

[1]*Departments of Surgery and* [2]*Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW*

Aims: To investigate whether the anaesthetic technique and post-operative provision of analgesia influence morbidity. Secondly, as POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) and Portsmouth correction (P-Possum) equally weight mild and severe complications, we define and analyse severe and mild complications, which may allow more accurate cross-group analysis.

Methods: A retrospective analysis of 148 patients' consecutive left-sided resections over a 25-month period was undertaken. Analysis of observed complication rate was compared to POSSUM expected morbidity and expected mortality; Portsmouth corrected mortality and correlation between type of anaesthesia/analgesia was also assessed.

Results: Expected (O:E) mortality was 0.359 (P-Possum 1.062), O:E morbidity 1.74. Of these 148 patients, only 15 received PCA. 46.3 per cent of observed morbidity was infective, 82.8 per cent was mild (pyrexia of unknown origin, urinary, chest or line), and 17.2 per cent severe (deep infection or septicaemia). Expected mortality and morbidity of patients receiving PCA and epidural were similar ($P=0.343$ and $P=0.348$). A greater infection rate is seen with epidural (45.1 per cent of which 18.4 per cent were severe) than in patients receiving PCA (20 per cent; χ^2: $P=0.02$), of which none were severe. 12.5 per cent patients receiving epidurals experienced hypotension (systolic <90 mmHg for >2 h; $n=17$), and of these all experienced complications and 58.9 per cent had septic episodes ($P<0.0001$).

Conclusions: Patients undergoing left-sided colonic resection and receiving epidural analgesia were more than twice as likely to experience an infective adverse event as those receiving PCA. This may in part be due to hypotensive episodes associated with epidural.

Colorectal 004

Prospective evaluation of a fast-track care pathway to reduce hospital stay after complex colorectal surgery

C.P. Delaney, A.J. Senagore, F.H. Remzi, A. Halverson, and V.W. Fazio (sponsor) P.R. O'Connell

Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA

Aims: Although attempts to reduce postoperative hospital stay are aimed at maximising efficiency of health care provision, multimodal care plans are generally reserved for noncomplicated colonic (and not rectal) resections. This study evaluates a 'fast-track' system for major colorectal surgery, and compares the results to traditional care plans used by other colorectal services in this institution.

Methods: Sixty consecutive patients (mean age 44.5 years, range 13–70) had major procedures over a 6-week period without NG tubes or epidural anaesthesia. Early diet and ambulation were encouraged. Discharge was after meeting defined criteria. Operations involved resection of rectum or ileal pouch–anal anastomosis (IPAA, $n=35$), IPAA or colo-anal anastomosis ($n=21$), colectomy ($n=19$), Koch pouch surgery ($n=6$), stricture-plasties ($n=5$), other ($n=5$). There were 22 defunctioning ileostomies.

Results: Fifty-eight patients (96.7 per cent) were suitable for 'fast-track' care and stayed 4.3±1.6 days postoperatively. Patients in DRG 148 (major bowel surgery with comorbidity, $n=40$) stayed 4.6±1.7 days, while patients in DRG 149 (without comorbidity, $n=18$) stayed 3.5±0.8 days ($P=0.01$). Three patients (5.2 per cent) required an NG tube for vomiting. None of four readmissions (6.9 per cent) within 30 days was attributable to 'fast-track' failure. Fast-track patients had a shorter stay than patients following traditional care pathways on other colorectal services during the study period and the subsequent two months (4.7 *versus* 7.7 days, $P<0.0001$).

Conclusions: The 'fast-track' protocol allows patients with high levels of comorbidity undergoing complex colorectal and reoperative pelvic surgery to benefit from a rapid recovery and early discharge from hospital. The approach is safe, successful, and has low readmission rates.

Colorectal 005

How accurate is POSSUM and p-POSSUM in predicting mortality in emergency surgery and in old age?

P.P. Tekkis,[1,2] H.M. Kocher,[3] N. Kessaris,[4] T.A. Harrison,[1] N. Slater,[2] A.J.M. Leather[3] and A.C.J. Windsor[4]

[1]*Greenwich District Hospital,* [2]*University Hospital Lewisham,* [3]*Kings College Hospital,and* [4]*St Mark's Hospital on behalf of the RISC Group of Hospitals*

Aims: The POSSUM and p-POSSUM equations were derived from a heterogenous general surgical population and have been successfully used as audit tools to provide risk-adjusted operative mortality rates. Their applicability to high risk, emergency colorectal surgery has not been validated.

Methods: POSSUM variables were recorded for 709 patients in six hospitals undergoing major elective ($n = 531$) or emergency ($n = 178$) colorectal surgery. Sub-group analysis was performed to investigate the predictive capability of POSSUM and p-POSSUM in emergency *versus* elective surgery and according to age groups.

Results:

	No of cases	Observed mortality (%)	P-POSSUM mortality (%)	POSSUM mortality (%)
Elective surgery	531	2.2	3.3	4.0
Emergency surgery	178	23.6	20.8	16.3
Age-group				
<50 years	179	0.6	2.6	3.1
51–60	116	2.5	3.5	4.8
61–70	164	6.1	7.7	8
71–80	176	12.5	12.8	12.2
>81 years	74	24.3	14.9	13.2
Total	709	7.6	7.8	7.9

Conclusions: POSSUM and p-POSSUM were found to accurately predict mortality in colorectal surgery as a whole, but were not suitable for subgroup analysis; both scoring systems had the tendency to overpredict mortality in the young and elective-patient group and underpredict deaths in the elderly and emergency cases. Suitable correction factors will need to be adopted to facilitate application of these systems to various patient subgroups.

Colorectal 006

The impact on survival of intensive follow-up after curative resection for colorectal cancer: a meta-analysis of randomized trials

A G Renehan,[1] M P. Saunders,[2] M Egger[3] and S T O'Dwyer[1]

Departments of [1]Surgery and [2]Clinical Oncology, Christie Hospital NHS Trust, Manchester, [3]Department of Social Medicine, University of Bristol, Bristol, UK

Aims: The value of intensive follow-up in patients after curative resection for colorectal cancer remains unproven, and consequently, current clinical guidelines range from suggesting no follow-up (Scotland) to inconclusive (England and Wales). We undertook a systematic review and meta-analysis of all randomized controlled trials (RCTs) examining the effectiveness of different follow-up strategies.

Methods: English and non-English RCTs were identified using electronic searches of MEDLINE, EMBASE, Cochrane Trial Registries, and CancerLit, supplemented by handsearching conference proceedings, selected articles and reviews. The primary outcome determined was cancer-related deaths from time of initial treatment. Secondary outcomes were detection of recurrences, resectability rates among recurrences, and disease-free rates following re-operation. Summary odds ratios (OR) were calculated using the fixed effect method.

Results: Five randomized controlled trials containing data on 1342 patients were included. Overall, for patients under intensive follow-up, there was a significant reduction in colorectal cancer-related deaths (OR = 0.75, 95 per cent CI, 0.59, 0.95). This equated to six lives saved for every 100 patients intensively followed (i.e. an absolute reduction of 6 per cent). The rates for first-relapse were similar for different strategies, but recurrent disease was detected significantly earlier in participants under intensive follow-up (mean difference = 8.5 months, 95 per cent CI 7.6, 9.47). This translated into resectability rates favouring intensive follow-up (pooled OR = 3.45, 95 per cent CI 1.95, 6.09), and in turn, improved crude salvage rates (pooled OR = 4.63, 95 per cent CI 1.45, 14.74).

Conclusions: The available cumulative data from RCTs support the view that intensive follow-up after curative resection for colorectal cancer improves cancer-related survival. Current guidelines should be re-addressed in light of the present findings.

ASGBI: Vascular 1–6 Thursday 26 April 2001 16:00–17:00

Vascular 001

Haemostatic markers before operation in patients with ruptured and acutely symptomatic nonruptured abdominal aortic aneurysm

D.J. Adam, P.C. Haggart, C.A. Ludlam and A.W. Bradbury

Vascular Surgery Unit and Department of Haematology, Royal Infirmary of Edinburgh, and University Department of Vascular Surgery, Heartlands Hospital, Birmingham, UK

Aims: In patients with acutely symptomatic but nonruptured abdominal aortic aneurysm (AAA), emergent repair is associated with an increased mortality rate compared with semielective repair. This study determines whether circulating markers of coagulation and fibrinolysis may distinguish ruptured and acutely symptomatic non-ruptured AAA.

Methods: Forty-four patients undergoing emergency AAA repair for acute symptoms and in whom ruptured AAA could not be confidently excluded on clinical grounds were studied prospectively. Tissue plasminogen activator (t-PA) activity, plasminogen activator inhibitor (PAI) activity, and prothrombin fragment (PF) 1+2 were measured prior to induction of anaesthesia.

Results: Ruptured AAA was confirmed at operation in 37 patients, and seven patients had acutely symptomatic non-ruptured AAA. Ruptured AAA was associated with significantly increased PAI activity ($P=0.002$) and PF 1+2 ($P<0.0001$), and significantly reduced t-PA activity ($P=0.02$). The differences in PAI activity ($P=0.002$), PF 1+2 ($P=0.008$) and t-PA activity ($P=0.008$) persisted when acutely symptomatic patients were compared with rupture patients who were normotensive.

Conclusions: These novel data demonstrate that acutely symptomatic AAA is associated with increased systemic fibrinolysis and reduced thrombin generation compared with rupture. The preoperative measurement of haemostatic markers may represent a useful adjunct to decision-making when attempting to distinguish patients with acutely symptomatic AAA from those with rupture.

Vascular 002

Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysms

T. Rowlands, A.I.D. Mavor, M.J. Gough and S. Homer-Vanniasinkam

Vascular Surgical Unit, The General Infirmary at Leeds, UK

Aims: Pro-and anti-inflammatory cytokine release (Th1/Th2 response) occurs with abdominal aortic aneurysm (AAA) repair though the relative contribution of each is currently poorly understood. Ischaemia–reperfusion injury (IRI) is thought to play a greater role following open (OR) than endovascular (ER) repair, with greater perioperative morbidity.

Methods: In 32 patients undergoing OR ($n=16$) and ER ($n=16$) of AAA, systemic blood taken at induction (baseline), 0 h (last clamp off), 4 h, 24 h, 72 h and 144 h, and femoral venous blood (indwelling catheter; lower torso direct venous effluent) at 0 h, 4 h, and 24 h, was analysed for interleukin (IL) −6, −8 and −10 (ethics approval).

Results: OR systemic (SV) and femoral (FV) venous IL-6 levels rose from baseline to peak at 24 h (SV 589 pg mL^{-1} $P=0.001$ *versus* FV 848 pg mL^{-1} $P=0.05$; Mann–Whitney) before declining at 144 h. ER patients showed a similar but reduced pattern (SV 260 pg mL^{-1} $P=0.003$ *versus* FV 319 pg mL^{-1} $P=0.06$ at 24 h). SV IL-6 was significantly elevated in OR above ER at all equivalent timepoints, with significantly greater FV IL-6 in the OR group at 24 h $P=0.007$. IL-8 peaked earlier (4 h) from baseline in both groups before declining by 144 h; raised FV *versus* SV levels of IL-8 were seen in both groups with no significant difference between them. IL-10 levels peaked in both groups at 24 h before declining at 144 h with no significant differences between the groups.

Conclusions: Proinflammatory SV and particularly FV cytokine release (IL-6) in OR is consistent with significant lower torso IRI. A lesser response was seen in ER (IL-6 and-8), though both groups showed a similar anti-inflammatory response (IL-10); this Th1/Th2 inbalance may account for the increased morbidity with OR.

Vascular 003

Endovascular abdominal aortic aneursym repair: the role of pre-operative embolization

D. Parry,[2] D. Kessel,[1] L. Denton,[1] I. Robertson,[1] J. Patel,[1] S. McPherson[1] and D.J.A. Scott[2]

[1]*Department of Vascular Radiology, and* [2]*Vascular Surgery, St James's University Hospital, Beckett St, Leeds LS9 7TF, UK*

Aims: To evaluate the affect of aortic side branch embolization on the incidence of endoleak following endovascular aortic aneurysm repair (EVAR).

Methods: A prospective evaluation of patients undergoing EVAR since 1997. All patients underwent preprocedural spiral CT scanning and calibrated angiography. Patent aortic sidebranches (inferior mesenteric artery and lumbar arteries) were identified. The inferior mesenteric artery was embolized in every case. Our current practice is to embolize patent lumbar arteries but initially this was not routine. Following EVAR patients were followed with ultrasound and dual phase spiral CT, the presence of endoleaks was recorded.

Results: Forty patients have undergone EVAR. The IMA was patent in 16 (45 per cent) patients. Lumbar arteries were patent in 21(53 per cent). IMA embolization was attempted in 13 patients and was successful in 11 (85 per cent), the IMA thrombosed during catheterization in the other 2 patients. Lumbar embolization was attempted in 13 patients and was successful in eight. There were no Type II endoleaks in any of the embolized patients. Eight out of 13 (62 per cent) patients with patent lumbar arteries developed endoleaks.

Conclusions: Type II endoleaks following EVAR occur in almost half of the patients with patent lumbar arteries. IMA and lumbar endoleaks are preventable by preoperative embolization.

Vascular 004

Prolonged renal ischaemia increases mortality in supra-renal abdominal aortic aneurysm patients

C.D. Bicknell, A.R. Cowan, M.I. Kerle, N.J.W. Cheshire, A.O. Mansfield and J.H.N. Wolfe

Regional Vascular Unit, St Mary's Hospital, London, UK

Aims: Elective juxta-renal abdominal aneurysm repair in our Unit has a significantly lower mortality than supra-renal abdominal aneurysm repair. Identification of factors affecting outcome may lead to reduction in mortality for supra-renal repair.

Methods: Data were collected prospectively between 1993 and 2000 for 127 and 61 patients undergoing elective supra-renal and juxta-renal aneurysm repair (SRAAA & JRAAA), respectively. Pre-operative risk factors: age, creatinine, gender, smoking, hypertension, diabetes, hypercholesterolaemia and ischaemic heart disease status were compared. Intra-operative factors: anaesthetic time, incision time, visceral ischaemia time, renal ischaemia time, lower limb ischaemia time, and intraoperative blood loss were related to outcome for the SRAAA group (there was only one death in the JRAAA group).

Results: In-hospital mortality was significantly higher following SRAAA than JRAAA repair (17.3 per cent *versus* 1.6 per cent). A raised serum creatinine was the only preoperative factor affecting mortality for SRAAA repair ($P=0.022$). Renal ischaemic time and anaesthetic time were significant factors in relation to mortality in SRAAA repair ($P<0.05$).

Conclusion: Impaired preoperative renal function and a prolonged renal ischaemic time were both related to higher mortality following supra-renal aneurysm repair.

Vascular 005

Perioperative risk factors and complications after elective abdominal aortic aneurysm repair

S. Dimitri, G. Mitchel, P.R. Edwards and L. de Cossart

Countess of Chester Hospital, UK

Aims: To assess the feasibility of predictive risk of death for elective repair of infrarenal abdominal aortic aneurysms using the POSSUM physiological score.

Methods: One hundred and two patients from DGH and 285 patients from the Vascular Surgical Society prospective database with complete data for POSSUM analysis who underwent standard elective surgery for an infrarenal aortic aneurysm surgery were analysed.

Results: In the DGH, Mean physiological scores (PS) were significantly greater in those who died (22.1 [SD 4.77] [CI 19.4–24.9] *versus* 16.4 [SD 4.30] [CI 16.0–16.9], $P<0.001$). Patients with a physiological score of 19 and above are at least 5 times as likely to die than those with PS below this [RR = 38.5 (5.3–278.7)]. The mean operative scores were also significantly higher in the deceased group 21.4, [SD 2.34][CI 20.0–22.7] *versus* 14.5, [SD 1.57][CI 14.1–14.8], $P<0.001$ Patients with operative score of 20 or above, had 6.8 RR of death [RR = 21.2 (6.8–66.8)] In the VSS patients mean physiological scores were also significantly greater in those who died 25.6, [SD 7.76] [CI 22.1–29.0] *versus* 20.1, [SD 5.42][CI 19.4–20.7], $P<0.001$. There was no significant difference in the mean operative scores of the dead and alive groups 19.0[SD 4.97][CI 16.75–21.16] *versus* 17.7, [SD 3.85] [CI 17.2–18.1], $P=0.153$.

Conclusions: The physiological score appears to be a useful preoperative predictor of death in patients undergoing AAA surgery and maybe useful to select patients for preoperative optimization.

Vascular 006

Acute symptomatic abdominal aortic aneurysms – immediate surgery does not compromise outcome

Z Raza, W. Stuart, J A. Murie, A.McL. Jenkins and R.T.A Chalmers
Vascular Unit, Edinburgh Royal Infirmary, Edinburgh, UK

Aims: The aim of this study was to establish the in-hospital operative mortality rate associated with symptomatic abdominal aortic aneurysm (AAA) surgery with reference to the urgency of operation

Methods: A retrospective analysis was carried out over a 5-year period (to June 2000) A total of 144 symptomatic AAAs were identified. Forty-six patients were treated electively and 98 were treated as emergencies Mortality rates of patients were compared with reference to the urgency of intervention (elective symptomatic, acute symptomatic <24 h, acute symptomatic >24 h)

Results:

			Acute symptoms		
	Elective *n* = 409	Elective symptoms *n* = 46	>24 h *n* = 70	<24 h *n* = 28	Ruptures *n* = 264
Mean age (year)	69	72	72	72	73
Sex (male percentage)	84	85	80	75	83
Mortality percentage	5.6	6.5	8.6	7.1	43.5

There was no significant difference in mortality rate between patients with acute symptomatic AAA who had surgery within 24 h (6/70 deaths) and those who had surgery delayed by at least 24 h (2/28 deaths).

Conclusion: Emergency operations for acutely symptomatic AAA do not carry excessive mortality compared to delayed surgery for preoperative assessment.

ASGBI: General 7–12 Thursday 26 April 2001 16:00–17:00

General 007

Competence day: development of a panel of objective assessment tasks for senior house officers at MRCS level

S. Mackay, V. Datta, P. Morgan, M. Mandalia, A. Chang and A. Darzi

Academic Surgical Unit, Imperial College School of Medicine, St Mary's Hospital

Aims: the objective assessment of surgical technical skill is an expanding area of research. This project aims to develop a panel of assessment tasks to assess technical competence in senior house officers (SHOs) at the MRCS level

Methods: Six separate tasks have been developed in the format of an OSCE (objective structured clinical examination) which takes 90 min to complete. The tasks are:

knot formation, and skin suturing (both assessed using electromagnetic motion analysis), excision of a skin lesion, and closure of an enterotomy (both assessed using OSAT techniques), laparoscopic tasks on the MIST VR simulator, and a test of instrument and suture knowledge. Subjects are SHOs and specialist registrars of differing levels, who perform component tasks according to seniority.

Results: Analysis is complete for comparisons between SHOs from years 1–3 (32 subjects). On the knot formation task and the suturing task, regression analysis of the relationship between time taken and number of movements demonstrates significant differences in the pattern of surgical performance across these two parameters ($P<0.001$, SPSS General Linear Model, univariate). These differences are observed despite the significant overlap between the groups, which renders non-significant the absolute difference for each parameter.

Conclusions: The use of regression analysis of surgical performance in terms of the relationship between time taken and number of movements is a potentially useful method of demonstrating competence in surgical training. This methodology has the capacity to avoid the problems of analysis created by a strong 'floor' effect in performance, and significant overlap between subjects in consecutive groups.

General 008

The effect of moderate alcohol consumption on the acquisition of laparoscopic surgical skills – a randomized controlled trial

S.G.T. Smith, T.J. Brown, J. Torkington and A. Darzi

The Department of Academic Surgery, Imperial College School of Medicine at St Mary's Hospital, UK

Aims: Alcohol misuse is well documented in the medical profession, but the effect of moderate alcohol consumption on patient care has never been formally documented. This study aimed to quantify the effect of drinking alcohol, up to the level of the UK legal driving limit, on the dexterity of those learning laparoscopic skills.

Methods: Twelve subjects, five surgical trainees and seven medical students, were pretrained on a computer-based simulation of a laparoscopic task, and on a standardized physical simulation of laparoscopic surgery. Each attended for trial on two occasions. On the first occasion they were randomized to consume alcohol (0.8 g alcohol kg^{-1} body weight in 2 pints of fruit juice) or placebo (0.1 g alcohol kg^{-1} body weight floated on 2 pints fruit juice), and were subjected to the other condition on the second occasion, forming a 2 × 2-crossover trial with subjects acting as their own controls. Subjects were assessed on both tests of laparoscopic dexterity pre-drink, and at hourly intervals for hours. Blood alcohol measurements were estimated using a conventional breathalyser. Dexterity measurements for both simulations were made using the Imperial College Surgical Assessment Device, a system of motion analysis whilst performing surgical tasks.

Results: Mean blood alcohol level was maximum at 1 h post drink, and was 77.9 ± 8.1 mg dL^{-1} (UK legal driving limit is 80 mg dL^{-1}). Virtual reality tasks revealed improved efficiency across repeated attempts in the placebo group. The alcohol group showed an initial depreciation in efficiency with a subsequent slow learning curve, such that significant differences in learning could still be detected 6 h after drinking ($P<0.036$, Mann–Whitney U-test). Analysing real tasks, placebos showed steadily improved performance across the repeat tests, in terms of less time and making faster but more efficient tool movements. The alcohol group showed an initial deterioration in performance, taking a longer time to complete the tasks, and making a greater number of less efficient movements. Significant differences were seen as early as ½ hour after drinking (37.6 per cent ± 9.4 deterioration in alcohol *versus* 7.3 per cent ± 6.2 improvement in placebo; $P<0.005$), and these differences remained for at least 6 hours after drinking (4.9 per cent ± 8.6 improvement in alcohol, 26.0 per cent ± 4.9 improvement in placebos; $P<0.02$). The differences were more marked when looking at the actions of the nondominant hand.

Conclusions: After drinking alcohol to a level that remains within the legal UK driving limit, significant differences in performance and learning of laparoscopic tasks can be shown. The effects on learning skills is sustained for at least 6 hours after consumption of alcohol, and such results might have implications on alcohol consumption guidelines for surgeons.

General 009

Relationship between skill and outcome in the laboratory based model

V.K. Datta, M.R. Mandalia, S.M. Mackay, A.A. Chang, N. Cheshire and A.W. Darzi

Academic Surgical Unit, Imperial College School of Medicine, UK

Aims: To demonstrate that objectively measuring differences in manual dexterity does have an impact on the outcome of a simulated surgical procedure.

Methods: Thirty vascular anastomoses were performed by six higher general surgical trainees of different levels of experience. Using a standardized technique on a vascular model, each trainee performed five consecutive end-to-side anastomoses of a polytetrafluoroethylene graft to a synthetic artery. Manual dexterity was objectively measured using: (1) electromagnetic motion analysis: trackers applied to the backs of hands recorded and analysed both hand movements and procedural time; and (2) a mini checklist score which evaluated steps of the procedure. Outcome parameters were assessed by: (1) rate of anastomotic leakage; and (2) cross-sectional area of the anastomotic graft.

Results: The two objective measures of manual dexterity correlated closely (Pearson coefficient of 0.413, $P<0.05$). Trainees with better manual dexterity scores produced better outcome measures. Those with better motion analysis scores produced anastomoses that leaked less (Pearson correlation coefficient of 0.514, $P<0.01$) and those with higher checklist scores had larger graft cross-sectional area (Pearson coefficient of 0.495, $P<0.01$). Time taken for the procedure did not appear to influence either outcome measure.

Conclusions: There is a significant correlation between objective measures of manual dexterity and the outcome measures, in this surgical simulation model. This suggests that the manual dexterity of a surgeon can influence the outcome of surgical procedures.

General 010

A national survey of consultant surgeons on perioperative fluid and electrolyte management

D.N. Lobo, M.G. Dube, K.R. Neal, S.P. Allison and B.J. Rowlands

University Hospital, Queen's Medical Centre, Nottingham

Aims: Perioperative fluid and electrolyte therapy in the UK is an area of concern that needs addressing urgently. This survey was designed to assess the attitudes of consultant surgeons to fluid and electrolyte prescribing practices and to garner suggestions for improvement in education and training on the subject in order to promote better management practices.

Methods: Postal questionnaires were sent to 1091 consultant Fellows of the Association of Surgeons of Great Britain and Ireland after an initial pilot. 730 (67 per cent) questionnaires were returned of which 20 were incomplete or invalid. 710 questionnaires were analysed.

Results: 60 per cent (424) respondents worked in district general hospitals (DGHs), 14 per cent (99) in associated teaching hospitals, 25 per cent (180) in main teaching hospitals and 1 per cent (7) in the private sector. Respondents had been consultants for a median (IQR) duration of 12 (6–18) years. Consultants in main and associated teaching hospitals were more likely to provide their junior staff with formal written guidelines on fluid and electrolyte prescribing than those in DGHs (27 per cent *versus* 19 per cent, $P=0.007$). 88 per cent of consultants provided their junior staff with informal verbal guidelines. Only 16 per cent of respondents felt that their preregistration house officers (PRHOs) and 54 per cent that their senior house officers (SHOs) had had sufficient training in fluid and electrolyte prescribing before joining the firm. 15 per cent also stated that PRHOs did not receive adequate training in fluid balance whilst on their firm. While 59 per cent of respondents always inspected fluid balance charts on ward rounds and 33 per cent inspected the charts frequently, only 65 per cent felt that they were accurately maintained. The most common reasons given for inaccurate charts were nursing shortages, nursing inefficiency and failure to appreciate the importance of fluid balance charts 38 per cent felt that patients received too much water, 11 per cent too little and 51 per cent about right. Corresponding figures for sodium and potassium were 26 per cent, 15 per cent and 59 per cent, and 1 per cent, 45 per cent and 54 per cent, respectively While 59 per cent of respondents preferred to err on the side of under-replacement of fluid in their postoperative patients, and 32 per cent on the side of over-replacement, 9 per cent felt that neither was acceptable Respondents who had been consultants for >5 years were more likely to err on the side of under-replacement of fluid than those who were consultants for ≤ 5 years (63 per cent *versus* 47 per cent, $P<0.001$) 20 per cent felt that early postoperative fluid balance was best managed by anaesthetists, 71 per cent by surgeons, 8 per cent by both and 2 per cent by others (such as nurse specialists). The most favoured suggestions for improvement in educational programmes on the subject included problem-oriented ward rounds, formal written guidelines for PRHOs and SHOs, and discussion of patient scenarios and management plans in the final year of medical school

Conclusions: Present practice in perioperative fluid management is unsatisfactory. Higher standards within clinical governance and risk management may be achieved by more practical training combined with formal written guidelines

General 011

For debate: revalidation of a pancreatic practice

I Daniels and E M. Chisholm

St Peter's Hospital, Chertsey, Surrey KT16 OPZ, UK

Reaccreditation and revalidation for organ specific procedures is currently exercising the minds of the great and the good We present a single-handed upper GI surgeon's audit of pancreatic cases over a 7-year period and ask you to consider whether you would reaccredit this practice

	Operation	Death
Necrosectomy	7	2
Pseudocyst (4 with resection)	7	0
Fistula (Distal Pancreatectomy)	2	0
Cancer Bypass	22	2 MI bleed
Local excision	3	0
Whipples	7	1 bleed

During the same period 112 consecutive oesophageal and gastric resections were performed with 4 deaths (3.57 per cent mortality rate) Would you accredit this practice? On which criteria should we judge these data? Who should determine these criteria, e g NICE, Augis, Royal Colleges? If accreditation is given what modifications/improvements would you wish to encourage? Answers on a postcard to your Medical Director, Chief Executive, GMC BMA please

General 012

Prevention of perioperative venous thromboembolism: outcome after cancer and noncancer surgery

A K Kakkar,[1] S Haas,[2] D Walsh[1] and A Encke[2]

[1]*Imperial College School of Medicine, London, UK and* [2]*Technical University, Munich, Germany*

Aims: Venous thromboembolism (VTE) is a common complication after cancer surgery Current methods for prevention may not offer sufficient protection to this high-risk population

Methods: Six thousand, one hundred and twenty-four patients with cancer and 16 954 without cancer undergoing major surgery were randomly allocated to receive unfractionated heparin (UFH) 5000 units three times daily or the low molecular weight heparin (LMWH) Certoparin 3000 units aXa once daily, both agents commenced preoperatively and continued for at least 5 and no more than 20 days after operation as part of the MC-4 Study

Results: By comparison to noncancer patients those with cancer had longer operations 124 6 *versus* 76 6 min (2p < 0 0001) Death within 14 days after the end of treatment with heparin occurred in 120/16 954 (0 71 per cent) of non-cancer and 192/6124 (3 14 per cent) of cancer patients (2p < 0 0001) Despite thromboprophylaxis the presence of PE at autopsy was confirmed in 0 41 per cent of cancer and 0.11 per cent of non-cancer patients (2p < 0 0001) with the overall rate of thrombosis being 1.26 per cent and 0 61 per cent, respectively (2p < 0 0001). Non-fatal PE was identified in 0 54 per cent of cancer and 0 27 per cent of non-cancer patients (2p < 0 0003) Patients with cancer had greater postoperative drain losses ($P = 0\ 0001$), higher requirements for transfusion of packed cells ($P = 0.006$) or whole blood ($P = 0\ 001$), more frequently underwent re-operation for bleeding ($P = 0\ 003$) and suffered more wound haematomas ($P = 0\ 001$) than non-cancer patients There were no differences in thromboprophylactic efficacy for cancer patients who received three times daily unfractionated heparin or once-daily LMWH Patients receiving LMWH had significantly lower transfusion requirements ($P = 0\ 031$).

Conclusions: These data indicate cancer operations are attended by a significantly higher early postoperative mortality than those for a benign pathology and that despite the adoption of currently advocated guidelines for VTE prophylaxis with UFH or LMWH, cancer patients remain significantly more likely to die due to postoperative pulmonary embolism The prevention of this avoidable complication in this high risk population requires further investigation

ASGBI: Transplantation 7–9 — *Thursday 26 April 2001 16:30–17:00*

Transplantation 007

Subtotal hepatectomy and temporary auxiliary liver transplant support: a new concept for toxic liver injury

M. Attia, N. Ahmad, K. Menon, K.V. Ravindra, K.R. Prasad, G.J. Toogood, S.G. Pollard and J.P.A. Lodge
Hepatobiliary and Transplant Units, St James's University Hospital, Leeds, UK

Aims: Toxic liver injury due to paracetamol overdose is the leading cause of fulminant hepatic failure in the U.K. There is no evidence for the development of chronic liver disease in the patients who survive this toxic injury without transplantation. Yet, despite maximal medical therapy, 5 per cent progress to emergency liver transplantation: 37 patients in our unit during April 1993-October 2000.

Methods: Beginning in June 1998 we have been piloting a clinical programme of subtotal (75 per cent) hepatectomy and auxiliary orthotopic liver transplantation for toxic injury: seven patients up to October 2000. Our technique is based on the following principles: (1) Subtotal hepatectomy to remove the 70–75 per cent of the injured liver; (2) transplantation of a maximal liver volume: a whole liver graft was used in all cases; (3) reconstruction by a piggy-back technique; (4) anastomosis of the donor portal vein and hepatic artery to the recipient right portal vein and hepatic artery; (5) donor biliary diversion to a Roux loop; [6] gradual withdrawal of immunosuppression after recovery.

Results: One patient died from lung injury at 24 h postoperatively and one died on day 8 with nonthrombotic graft infarction. Four patients are alive off immunosuppression at 9, 25, 26 and 32 months and a fifth is recently postoperative (3 months). Native hepatic function and regeneration with transplant atrophy has been confirmed by isotope scanning and CT scanning in the long term survivors.

Conclusions: Results with this new technique are encouraging. Our technique allows the patient to return to a normal life within a few months.

Transplantation 008

Rising incidence of post transplant lymphoproliferative disease in kidney transplant recipients transplanted at a single centre

G. Libertiny, C.J.E. Watson, D.W.R. Gray, K.I. Welsh and P.J. Morris
Oxford Transplant Centre, Churchill Hospital, Headington, Oxford OX3 7LJ, UK

Aims: To determine if the incidence of post transplant lymphoproliferative disease (PTLD) has been increasing among renal transplant recipients in Oxford, and if this was the case, what causes can be found.

Methods: Prospectively gathered data were analysed to establish trends in the epidemiology of PTLD among 1537 patients transplanted between January 1975 and June 1998.

Results: Overall, PTLD occurred in 2.3 per cent. An increase in its incidence coincided with the introduction of cyclosporin in the 1980s ($P=0.03$). However, there was a further increase in the incidence of PTLD in the 1990s ($P=0.03$) when the only change in immunosuppressive policy was the abandonment of pretransplantation blood transfusion. The latter increase was particularly pronounced in cases of early onset PTLD when it presented within 600 days after transplantation ($P=0.013$). With logistic regression analysis PTLD was more common among patients whose original cause of the renal failure was unknown ($P=0.05$) and whose serum creatinine level was 135–160 µmol L^{-1} compared with higher and lower creatinine values 2 years after the transplantation ($P=0.016$).

Conclusions: The incidence of PTLD has been increasing among renal transplant recipients. The recent increase appears to be independent of cyclosporin and may reflect the reduction in pretransplant blood transfusion.

Transplantation 009

Ex vivo split liver transplantation – complications and outcome

H.M. Noujaim, M. Fink, B.K. Gunson, D. Candinas, D.A. Mayer, J.A.C. Buckels, J. De Ville De Goyet, P. McMaster and D.F. Mirza
Liver Unit, Queen Elizabeth Hospital and Birmingham Children Hospital, Birmingham, UK

Split liver transplantation (SLT) is an option to improved utilization of the liver donors' pool. In 1998 we instituted an intention to split policy with simultaneous paediatric and adult transplantation.

Aims: Analys is of the complications and outcome of *ex vivo* (SLT).

Methods: Between Nov/92 and July/2000, 46 *ex vivo* split liver procedures (SLP) were performed at our institution, resulting in 92 grafts, 13 of these were exported to other centers and four grafts were imported. We performed 83 SLT, 29 SLT before 1998 (group I) and 54 SLT after 1998 (group II), in 32 adults and 49 children. In 50 donors, median age was 26 (7–54) years, median weight – 60.5 (22–100) kg; median days in mechanical ventilation 2.5 (0.45–8) and median of level AST was 52 (6–200)U L^{-1}. The recipients parameters analysed were: age, sex, blood group, UNOS status, transplant indication, segments used, cold and warm ischaemic time, peak AST, bilirubin and INR during 5 days after SLT. The vascular and biliary complications, primary non-function (PNF), bleeding and patients and graft survival were analysed and compared.

Results:

	Group I (29 SLT/28 patients)	Group II (54 SLT/53 patients)	*P*
Age (years)	25.7 (0.6–58)	22.7 (0.038–65)	ns
UNOS status (IV)	18 (64.3%)	39 (73.6%)	ns
CIT (minutes)	910 (435–1326)	720 (395–1086)	0.007
WIT (minutes)	36.1 (22–60)	41.8 (22–64)	0.03
AST (U L^{-1})	1266 (117–10000)	740 (150–6961)	ns
INR	1.5 (1–2.8)	1.4 (1–2.6)	ns
Vascular complications	5 (17.2%)	4 (7.4%)	ns
Biliary complications	6 (20.7%)	10 (18.5%)	ns
PNF	4 (13.8%)	0	0.01
Bleeding	1 (3.45%)	3 (5.5%)	ns
Patient survival (1 year)	72.5%	86.5%	0.04
Graft survival (1 year)	60%	80%	0.03

Conclusions: Implementation of an intention to split policy with simultaneous recipient procedures reduced cold ischaemic time and improved outcome following SLT.

ASGBI: Six of the Best Vascular

Friday 27 April 2001 09:15–10:15

Vascular 007

Ruptured abdominal aortic aneurysms in a remote and rural area

K. Cassar, D.J. Godden[1] and J.L. Duncan

Department of Surgery, Raigmore Hospital, Inverness, and [1]Highlands and Islands Health Research Institute, Raigmore Hospital Inverness, UK

Aims: There are few reliable data on the effect of transfer of patients with ruptured abdominal aneurysm on mortality. The aim of this study was to evaluate the effect on mortality of transfer of such patients over considerable distances in a sparsely populated area.
Methods: Patients who had a ruptured abdominal aortic aneurysm in the Highland region between 1/1/1992 and 31/12/1999 were identified retrospectively from departmental, theatre and hospital records. Visitors and patients who lived outside the Highland region were excluded. Death certification data were obtained from the Registrar General for Scotland. These data were cross-checked with information from the Information and Statistics Division of the National Health Service in Scotland.
Results: Between 1992 and 1998, 198 ruptured abdominal aortic aneurysms were diagnosed in the Highland region, an area the size of Wales or Belgium and with a population of 204 000 (12.1 deaths per 100,000 per year). 131 patients were treated at Raigmore Hospital, Inverness, 35 died in community hospitals and 32 died at home. 109 patients proceeded to surgery. The community mortality was 67 per cent, hospital mortality 50.4 per cent and the operative mortality was 40.4 per cent. Out of 116 patients reaching Raigmore Hospital, 81 had travelled less than 50 miles while another 35 had travelled more than 50 miles. The hospital mortality in Raigmore Hospital for those travelling less than 50 miles was 60 per cent while for those travelling more than 50 miles it was 35 per cent. The community mortality for patients living within 50 miles of Raigmore hospital (67 per cent) was however, almost identical to that for those living beyond 50 miles of Raigmore (68 per cent).
Conclusions: The community hospital and operative mortality for ruptured abdominal aortic aneurysms in a remote and rural area is comparable to results in urban areas. The distance travelled to the hospital had no significant impact on community mortality.

Vascular 008

Intra-abdominal pressure is elevated in patients following surgery for ruptured abdominal aneurysms

M. Anderton, V. Papavassiliou, N. London, R. Naylor, P.R. Bell and M.M. Thompson

Department of Surgery, Leicester Royal Infirmary, UK

Aims: Successful repair of ruptured abdominal aortic aneurysm (rAAA) carries a high postoperative mortality due to multiple organ failure (MOF), and studies from trauma centres in the USA have implicated elevations of intra-abdominal pressure (IAP) and the abdominal compartment syndrome (ACS) in the development of MOF following abdominal trauma. The aim of this study was to determine abdominal pressure in patients following endovascular, elective conventional and ruptured aneurysm surgery.
Methods: Data were collected prospectively for all patients admitted for elective aneurysm repair, between February and November 2000. The number of patients in each group is shown in the table below. Two of the elective conventional repair group were female, and all other patients were male. One patient died (elective conventional repair group). There was no significant difference in ages in the three groups (mean (s.d.) = 70.9 (7.3), 74.4 (5.4), 72.3 (4.27) for elective conventional, endovascular and emergency, respectively). Intra-abdominal pressure was measured daily using intravesical manometry.
Results: The results are tabulated below as median values with interquartile ranges. Statistical analysis compared each group with the elective conventional group and utilizes Mann–Whitney tests.

	Median	(IQR)	*P*-value
Day 0			
EVAR (*n* = 7)	5.0	(6.0)	0.051
Elective conventional repair (n = 18)	9.5	(4.25)	–
rAAA repair (n = 7)	21.0	(8.0)	0.02
Day 1			
EVAR (*n* = 7)	9.5	(4.5)	0.075
Elective conventional repair (n = 18)	13.0	(11.25)	–
rAAA repair (n = 7)	16.0	(8.0)	0.350
Day 2			
EVAR (*n* = 7)	–	–	–
Elective conventional repair (n = 18)	13.5	(8.5)	–
rAAA repair (n = 7)	14.0	(5.5)	0.79

EVAR, endovascular aneurysm repair

Conclusions: The results show that following repair of rAAA, the IAP was significantly higher than either following EVAR or elective repair, and that over subsequent days this difference diminishes. Early intervention has been shown to dramatically improve outcome in patients with abdominal compartment syndrome, and this study provides evidence that raised intra-abdominal pressure may contribute to the outcome of surgery for ruptured abdominal aneurysms.

Vascular 009

Endovascular aortic repair: has there been an improvement in device performance?

S.J. Holtham, S. Dugdill, J. Rose, T.A. Lees and M.G. Wyatt

Northern Vascular Centre, Freeman Hospital, Newcastle Upon Tyne, UK

Aims: Endovascular aortic repair (EVAR) is a relatively new procedure with continuing development in the design of the device itself. The aim of this study was to identify whether these improvements have resulted in better device performance between the first commercially available stent and a later generation device.
Methods: Between December 1995 and July 1999, 55 Vanguard devices were deployed. These results were compared with 51 patients who received a Zenith device, between September 1998 and October 2000. All follow-up was according to the Eurostar criteria.
Results: The mean age of patients receiving a Zenith device was slightly greater than the Vanguard cohort (73.8 ± 6.3 years *versus* 70.6 ± 8.6 years, $P = 0.04$) as was the mean aneurysm diameter (68 ± 15 mm *versus* 60 ± 9 mm, $P = 0.002$). There was no difference between the two groups with regard to operation time, ASA grade, intraoperative blood loss or hospital stay. In the Vanguard cohort, with a median follow-up of 24 months (range 6–48 months) there were 11 deaths, one due to a ruptured abdominal aortic aneurysm, 11 (21.6 per cent) occluded graft limbs and eight (15.7 per cent) endoleaks. In the Zenith cohort, with a median follow-up of 12 months (range 1–24 months) there were three deaths, none related to the AAA, one type II endoleak and one limb occlusion. The cumulative endoleak free survival rate and intervention free survival rate at 12 months was 98 per cent and 96 per cent, respectively, for the Zenith device. The Vanguard, at 12 months, was 94 per cent and 82 per cent, respectively. The maximal aneurysm diameter at 12 months in the Zenith cohort had decreased by 12.2 per cent and in the Vanguard cohort by only 3.6 per cent.
Conclusions: The durability of the Zenith device appears to be greater than that of the first generation devices with fewer secondary interventions and there is a significant reduction in the aneurysm sac following the procedure. Longer follow-up is essential to determine the long-term durability.

Vascular 010

No recurrence of reflux following endovascular radiofrequency ablation of the long saphenous vein (VNUS Closure) at one year

N. Fassiadis, B. Kianifard, J.M. Holdstock and M.S. Whiteley

Department of Vascular Surgery, Royal Surrey County Hospital, Guildford, UK

Aims: High long saphenous vein (LSV) tie in combination with stripping of the LSV remains the mainstay of treatment despite recurrence rates of 20–40 per cent. This study demonstrates our experience with the VNUS Closure, a novel endovascular computer-feedback-controlled application of bipolar electrothermal energy that ensures transmural heating of the vein wall while minimizing thermal spread to neighbouring tissues.
Methods: Seventy-nine patients (61:18 F:M, age 22–92, mean 42.2 years) had 127 legs treated between March 1999 and October 2000. One additional patient, early in the series and treated for ulceration only, had immediate failure of closure and proceeded to open surgery. All other operations were for varicose veins, 28 legs were recurrent, four legs had concomitant ulceration and 21 legs were treated with additional SEPS.

Results: Post-operative LSV closure on duplex ultrasound.

	No. of legs
	127
Immediate	127 (100%)
6 weeks	80 (100%)
3 months	51 (100%)
6 months	42 (100%)
12 months	28 (100%)

All patients were fully mobile within 12 h and all patients returned to their daily activities or to work within 72 h apart from one patient who complained about lateral thigh pain unrelated to the procedure. All 28 patients who underwent a full venous incompetence study at 1 year postoperatively showed no recurrence in the LSV. One patient developed reflux in a lateral thigh branch that had its origin in the common femoral vein.

Conclusions: This novel method of radiofrequency ablation provides not only a minimal access alternative to the classical high saphenous tie and strip but our results to date show no recurrence in the treated LSV. The only recurrence found was new reflux in a lateral thigh branch that we now treat with the VNUS system at the time of LSV surgery.

Vascular 011

Restenosis after iliac interventions: the reality

S. Bhasker, D.J.A. Scott, D.C. Berridge, P.J. Kent, R.C. Kester, J. Patel, D. Kessel and I. Robertson

Department of Vascular and Endovascular Surgery and Department of Vascular Radiology, St James University Hospital Leeds, UK

Aims: To assess the safety and durability of endovascular interventions for iliac occlusive disease.

Methods: The Department of Vascular Radiology computer database was interrogated to identify 77 consecutive patients who had undergone either angioplasty or stent placement for iliac occlusive disease. The patients were followed up with duplex ultrasound scan at 6-monthly intervals or more frequently if clinically indicated. The anatomic patency of the treated iliac segment in 40 patients who had more than 12 months follow up with duplex scan were analysed. Statistical analysis was by χ^2 analysis with Yates correction.

Results: The median age was 70 years (48 men and 29 women). 115 iliac segments (70 common iliac artery, 40 external iliac artery) in 104 limbs were treated. 41 patients (61 iliac segments) were stented. The immediate technical success was 94 per cent. 15 patients (19.4 per cent) developed complications of whom seven patients were managed by stent placement. Three patients needed urgent surgical intervention. There were no deaths within 30 days. 40 patients had a follow-up of over 12 months (median 22.5 months.). In the overall group (PTA alone and stenting) restenosis was noted in 36 per cent of treated external iliacs, 20 per cent of common iliacs and in 64 per cent when both were treated ($P < 0.001$). By contrast in the stent group alone, restenosis was noted in 20 per cent of external iliac arteries stented, 22 per cent of common iliacs and in 43 per cent of combined CIA/EIA lesions (not significant).

Conclusions: Iliac angioplasty and stenting are safe procedures with a high technical success rate. However, endovascular treatment of occlusive lesions of external iliac artery alone or in combination with common iliac artery lesions had a much higher rate of restenosis irrespective of stenting.

Vascular 012

Inter-hospital provision of emergency vascular services for a large population: early outcomes and clinical results

R.N. Baird,[1] A.R. Baker,[3] C. Hine,[4] P.M. Lamont,[1] P.A. Lear,[2] E. Loveday,[2] D.M. Mitchell,[2] M. Morse,[3] E.N. Munro,[3] K.P. Murphy,[1] M.R. Rees,[1] F.C.T. Smith and M.J. Thornton[2]

Departments of Surgery & Radiology, [1]Bristol Royal Infirmary, [2]Southmead, and [3]Frenchay Hospitals and [4]Avon Health Authority

Aims: In 1999, a collaborative emergency vascular service for Bristol and Avon (including Weston-Super-Mare) (population approximately 1 million) was initiated, involving Bristol Royal Infirmary, Frenchay and Southmead Hospitals. The aim of the rota was to accommodate NCEPOD and VSS recommendations, overnance issues and to enhance emergency vascular care for Avon residents.

Methods: Clinical data for the first year of the rota (May 1999-April 2000) were collected prospectively.

Results: There were 289 emergency admissions. (In-hospital referrals were not transferred but contributed up to 40 per cent extra emergency workload per unit). Referrals were accepted from seven Trusts outside the designated catchment area. Case-load included 86 ruptured/acutely symptomatic AAAs of which 69 underwent operation (30.4 per cent mortality). 136 patients had critical leg ischaemia (43 acute; 93 chronic); angiography/duplex was obtained in 105 (77.2 per cent); 39 (28.7 per cent) had undergone previous intervention for PVD; mortality was 18/136 (13.2 per cent); 18/136 (13.2 per cent) of patients required amputations. Other emergency cases included upper limb ischaemia – 20 (6.9 per cent); paediatric emergencies – seven (2.4 per cent); symptomatic carotid disease – five (1.7 per cent) (four endarterectomies – nil mortality/CVA). 5 per cent of referrals were inappropriate (venous ulcer; spinal stenosis, etc.). No outcome was compromised by interhospital transfer. Vascular surgeons operated on nine high-risk patients away from their 'base' hospital. A consultant was principal or assistant operator in >95 per cent of cases but despite trainee rota adjustments, a designated vascular trainee was only present in approximately 40 per cent of cases.

Conclusions: Inter-hospital provision of emergency vascular services for a large population is feasible, does not compromise quality of care and regulates emergency workload. Further attention to training issues is indicated.

ASGBI: Colorectal 7–15

Friday 27 April 2001 09:15–10:45

Colorectal 007

Outcome of operations for cryptoglandular anorectal fistula; predictive factors for impairment of continence

E. Mylonakis, D.G. Morton, S. Radley and M.R.B. Keighley

University Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK

Aims: This prospective study explored the predictive factors for impaired continence after surgical treatment of cryptoglandular anorectal fistulas (AF).

Methods: One hundred and twenty patients with AF were recruited (49 women), none had inflammatory bowel disease or previous fistula operations. Continence assessment and anal manometry were used in all patients before and three months after operation. Surgical treatment consisted of fistulotomy 74, fistulectomy two and cutting seton 44. Follow up was 1.8 years (range 0.9–2.6). Patients with low preoperative anal pressure or women with anterior trans-sphincteric fistula were treated by seton. Fistulotomy was confined to intersphincteric and low trans-sphincteric fistula. None of the patients had any impairment of continence before the fistula operation.

Results: Twenty-eight patients (23 per cent) developed incontinence (flatus 10, liquid four and soiling 14), 16 after fistulotomy (21 per cent), 11 after seton (25 per cent) and 1/2 after fistulectomy. More incontinent patients were women (57 per cent *versus* 45 per cent, $P=0.02$) or patients over 50 years of age (50 per cent *versus* 31 per cent, $P=0.01$). The only significant fall ($P<0.05$) in resting and squeeze anal pressure were in patients treated by fistulotomy for trans-sphincteric fistula (110.1 ± 8.4–84.1 ± 12.4, 223.5 ± 29.7–149.8 ± 32.5, respectively). Eight patients developed recurrent fistula; fistulotomy 6/74, seton 2/44.

Conclusions: Females and patients over 50 are susceptible to incontinence which can occur with all methods of AF treatment but fistulotomy should probably be avoided in trans-sphincteric fistula and patients treated by cutting seton should also be warned about the risk of incontinence.

Colorectal 008

Diltiazem heals GTN-resistant chronic anal fissures

M. Jonas, W. Speake, J. Simpson, T.J. Varghese and J.H. Scholefield

University Hospital, Queen's Medical Centre, Nottingham, UK

Aims: Treatment of chronic anal fissures is directed at lowering resting anal pressure (RAP). Glyceryl trinitrate (GTN), a nitric oxide donor, lowers RAP and heals 60–70 per cent of chronic fissures. Topical diltiazem, a calcium channel blocker, also lowers RAP, this study evaluated its efficacy for fissures failing to heal with GTN.

Methods: Consecutive patients with fissures despite using 0.2 per cent GTN ointment underwent anal manometry before and for 1 h after application of 700 mg of 2 per cent diltiazem gel to the distal anal canal. Patients applied diltiazem twice daily for 8 weeks. At fortnightly review, fissure healing was assessed and side-effects noted. Patients represented pain, bleeding and irritation on visual linear analogue scales at the initial and follow-up visits.

Results: In 39 patients (13 male), median age 42 years, topical diltiazem lowered RAP by 20 per cent from a median of 93–74 cm H_2O ($P<0.001$), and fissures healed in 19 (49 per cent) patients within 8 weeks. Most patients [27 (69 per cent)] had previously completed a course of GTN. Twelve had discontinued GTN prematurely or used less than recommended because of headaches, and of these 7 (58 per cent) healed with diltiazem, and five (42 per cent) did not. Four (10 per cent) patients developed side-effects: three reported mild perianal itching, and one discontinued diltiazem after 6 weeks because of headaches, drowsiness and mood swings.

Conclusions: Topical diltiazem is effective treatment for chronic fissures even where GTN has failed.

primarily perianal itching, occurring in 10 per cent but generally tolerated

Colorectal 009

Iron-deficiency anaemia and delay in the diagnosis of colorectal cancer

T. Al-Mishlab, P. Acher and T. Bates

Department of Surgery, William Harvey Hospital, Ashford, Kent
TN24 OLZ, UK

Aims: Iron-deficiency anaemia is a recognized complication of colorectal cancer especially with right-sided tumours and failure to investigate the anaemia in older patients may lead to a delay in diagnosis. The aim of this study was to establish the proportion of patients with colorectal cancer (CRC) shown to have an iron-deficiency anaemia (IDA) more than 6 months or 1 year before the diagnosis of cancer was made.

Methods: All patients presenting with confirmed colorectal cancer in a health district (catchment population 280 000) in the 4 years 1996–9 were identified from the pathology database after ethical approval. The criteria for IDA were $\text{Hb}<10.1\ \text{g dL}^{-1}+$ mean corpuscular volume <78 fl and/or mean corpuscular haemaglobin concentration $<32\ \text{g dL}^{-1}$. The haematology database serving the same population was searched for evidence of (i) IDA at diagnosis of colorectal cancer; ii) IDA more than 6 months and more than 1 years before the diagnosis of CRC, and iii) the number of haematology referrals in women over 55 and men over 50 years of age meeting the criteria for IDA.

Results: Of 299 patients with colorectal cancer, 111 (37 per cent) had IDA at diagnosis and of the latter 35 (12 per cent) were known to have IDA 6 months before diagnosis and 18 (6 per cent) had IDA more than 1 year before diagnosis. IDA was more common in right-sided tumours (76 per cent) than in those arising in the left side of the colon or the rectum (22 per cent). The annual incidence of IDA in the sampled population was 492 in the stated age-group.

Conclusions: The investigation of iron-deficiency anaemia in older patients is important but in order to detect 18 patients with colorectal cancer a year earlier, the investigation of *c.* 2000 patients would be required, a detection rate of less than 1 per cent.

Colorectal 010

A scoring system to prioritize colorectal referrals

S.N. Selvachandran, R. Dey, R. Hodder and D. Cade

Leighton Hospital, Crewe, Cheshire, UK

Aims: To design a program to accurately predict those patients at high risk of colorectal cancer based on primary symptoms and a scoring system derived from a Patient Consultation Questionnaire (PCQ).

Methods: A prospective study was initiated in 1999 in which 1133 patients referred by their GP, filled in a PCQ linked to an electronic patient record. A numerical score was derived from weighting the primary symptoms and symptom complexes. The scoring system was assessed statistically using the ROC curve and compared with a logistic regression derived model.

Results: Of the 1133 patients, 37 had CRC. The average score of the cancer patients (79.4) was significantly higher than the non-cancer patients (39.9) with a *P*-value <0.00001. 32 cancer patients (86.5 per cent) scored above 60 and 202 of the total patients (17.8 per cent) scored above 60. When using a cut-off point of 60 the scoring system had a sensitivity and specificity of 86.5 per cent and 84.5 per cent, respectively.

Conclusions: Using the PCQ and scoring system only 17.8 per cent of patients with colorectal symptoms would need to be assessed urgently to detect 86.5 per cent of the cancers. This system could help to achieve the 2-week rule, is easy to use, highly sensitive and specific with a high predictive value and is an efficient modality for fast tracking CRC.

Colorectal 011

Obscure gastrointestinal bleeding – a DGH experience

A.G. Heriot and N.D. Karanjia

Department of Surgery, Royal Surrey County Hospital, Guildford, UK

Aims: Gastrointestinal bleeding where a diagnosis is not readily obtained on routine endoscopy is rare but does represent an important group of patients with significant mortality and resource implications. The aim was to assess the pathology, management, resource implications, and outcome of these patients in a district general hospital.

Methods: The notes of all patients with gastrointestinal bleeding that remained undiagnosed following routine endoscopy (OGD/colonoscopy) presenting to a single consultant with an interest in obscure gastrointestinal bleeding over a 5-year period were reviewed with respect to intervention, diagnosis, and outcome.

Results: Twenty consecutive patients (13 male, seven female), with a mean age of 61 years (SD 18), were seen during this period. Forty percent presented with iron deficiency anaemia and 60 per cent with gastrointestinal bleeding. An escalating series of investigations (total number) were applied including repeat OGD (40) and colonoscopy (21), CT scan (nine), mesenteric angiogram (15), and radiolabelled red blood cell scan (two). No site of bleeding was identified prior to laparotomy in 20 per cent of cases and 80 per cent of cases proceeded to laparotomy (18). On-table endoscopy was required in six cases. The site of pathology was stomach (5 per cent),

pancreas (5 per cent), 2nd part duodenum (5 per cent), 3rd/4th part duodenum (30 per cent), jenunum/ileum (30 per cent), right colon (10 per cent), left colon (10 per cent), and maxillary sinus (10 per cent). The pathology was malignant in 35 per cent of cases. Eighty percent required a bowel resection and a definitive diagnosis was made in all patients with no further bleeding at a mean follow-up of 5 months (SD 5).
Conclusions: Diagnosis of obscure gastrointestinal bleeding requires extensive investigation with a proportion necessitating diagnostic laparotomy. Identification of the source and outcome can be successful if a logical progression of investigations including laparotomy and on-table endoscopy is followed.

Colorectal 012

Is intravenous fluid replacement indicated during bowel preparation for colonic surgery?

G. Sanders, S.J. Mercer, K. Saeb-Parsey, M.A. Akhavani, K.B. Hosie and A.W. Lambert
Department of Surgery, Derriford Hospital, Plymouth, UK

Aims: Bowel preparation using purgatives has previously been shown to significantly increase haemoglobin concentration and decrease weight. This prospective randomized study assesses the effects of administering calculated intravenous fluid during bowel preparation.
Methods: During bowel preparation for colonic procedures using Picolax (Ferring Pharmaceuticals Ltd, Berkshire), patients were prospectively randomized to receive no intravenous fluid (group 1) or calculated intravenous normal saline (group 2), based on body weight. Physiological, haematological and biochemical parameters were measured before and after preparation.
Results: Forty-one patients were recruited with a median age 69 years (range 29–86), group 1 $n = 22$, group 2 $n = 19$. There was no difference between groups prior to bowel preparation. On completion, there was a significant difference between groups for mean weight loss ($P = 0.01$), postural drop in systolic pressure ($P = 0.015$), and, serum creatinine rise ($P = 0.008$). In addition there was a significant difference within group 1 for weight loss ($P < 0.001$), drop in erect systolic pressure ($P = 0.011$), drop in erect diastolic pressure ($P = 0.023$), and drop in supine diastolic pressure ($P = 0.005$). Serum potassium concentration decreased significantly in groups 1 and 2, $P = 0.019$ and $P < 0.001$, respectively. The mean urine output in group 1 was 982 mL and group 21808 mL ($P = 0.004$) but the faeces weight was not significantly different ($P = 0.93$).
Conclusions: Picolax bowel preparation causes a significant dehydrating effect, which can be minimized by administering a simultaneous calculated volume of intravenous fluid. Consideration should also be given to potassium replacement.

Colorectal 013

Vitamin B12 deficiency after ileoanal pouch formation – what is the cause?

D.B. Coull, J.H. Anderson, R.F. McKee and I.G. Finlay
Department of Coloproctology, Glasgow Royal Infirmary, UK

Aims: To identify the incidence of serum B12 deficiency after totally stapled restorative proctocolectomy (TSRP) and establish whether it occurs secondary to bacterial overgrowth or terminal ileal resection, and how B12 should be replaced within this patient group.
Methods: Vitamin B12 levels were measured in our group of 164 patients, at regular follow-up, after TSRP. Hydrogen breath tests and Schilling tests, respectively, were performed to investigate whether bacterial overgrowth or resection of the terminal ileum, were responsible for subnormal B12 levels.
Results: At follow-up, 39 patients (23.8 per cent) had low B12 (< 188 pg mL^{-1}), at a median of 2.4 years (0–7) of pouch function. In addition 47 (73.4 per cent) patients with multiple B12 measurements showed steadily decreasing levels. 34/35 (97.1 per cent) patients with B12 deficiency who subsequently had a hydrogen breath test were negative for bacterial overgrowth, and none (0 per cent) of these patients had an abnormal Schilling test result.
Conclusions: Most patients show a decreasing trend in serum B12 levels following TSRP, and within 7 years, almost a quarter of patients will have subnormal B12 levels. Neither bacterial overgrowth, nor terminal ileal resection appear to be the cause of B12 deficiency in this study, and the normal Schilling test results suggest that these patients could be treated effectively with oral vitamin B12 supplementation.

Colorectal 014

Functional outcome and quality of life following the formation of an antegrade colonic enema in patients with constipation and faecal incontinence

P. Mackey, L. MacDonald, N.D. Carr and J. Beynon
Department of Colorectal Surgery, Singleton Hospital, Swansea, Wales, UK

Aims: The aim of this retrospective review was to assess functional outcome and quality of life following the formation of an antegrade colonic enema (ACE).
Methods: All patients who had undergone an ACE procedure at a district general hospital were identified. Their level of continence was assessed using the Cleveland Continence Scoring (CCS) and quality of life was assessed using the SF36. Irrigation patterns and complications related to the ACE were also identified.
Results: Nine patients (four male, five female) were identified. The mean age was 29 years (range 9–55). The indications for the formation of an ACE were megarectum (three), slow transit constipation (four) and imperforate anus (two). CCS improved from 15 (range 8–20) preop to 4 (range 0–10) postop. The postop mean SF36 quality of life score was 102 (range 76–138), indicating that most patients derived great benefit in their overall health since having undergone the ACE formation. Seven patients were considered a success, but all patients were troubled by mucus leakage.
Conclusions: In selected patients the ACE procedure provides a marked improvement in bowel function and quality of life. The ACE is a relatively minor procedure and is well tolerated but if it proves unsuccessful it is easily reversible without jeopardising further surgical treatment options

Colorectal 015

Surgery for rectal urgency – quality of life and symptom analysis results for a new procedure

C.L.H. Chan, T. Tillin, S.M. Scott, P.J. Lunniss and N.S. Williams
Academic Department of Surgery, Barts & The London School of Medicine & Dentistry, UK

Aims: Severe incapacitating rectal urgency, associated with faecal incontinence, can have a profound debilitating effect on patients' lifestyles, and is an extremely difficult condition to manage as there are no established therapies. We present quality of life and symptom analysis results at 1 years, of patients undergoing a novel surgical procedure (rectal augmentation) pioneered in our unit for this condition (*Dis Colon Rectum* in press).
Methods: Six patients (five female) with marked rectal urgency, who underwent rectal augmentation, utilizing a segment of distal ileum, were studied. In five of the patients, the procedure was in combination with stimulated gracilis neosphincter reconstruction. Quality of life and symptom data were collected prospectively using validated scoring methods (Hospital Anxiety Depression index, Nottingham Healthcare Profile, Royal London Hospital). Data was evaluated by an independent assessor. This study was approved by the Local Ethics committee.
Results: Following surgery, all patients described a rapid loss of rectal urgency, which was maintained over the year. Five patients have had successful closure of their defunctioning stomas. All quality of life instruments used showed a statistically significant improvement in patients' scores and wellbeing ($n = 4$). This appeared to correlate well with an improvement in postoperative anorectal physiological assessment, notably a significant increase in maximum tolerable volume. No major postoperative complications were noted.
Conclusions: In patients with debilitating urgency of defecation, creation of a neo-rectal pouch abolishes these distressing symptoms of rectal urgency almost instantaneously, and this is maintained after closure of the defunctioning stoma. We have demonstrated a significant improvement in quality of life at 1 year. Rectal augmentation represents a novel, safe and successful form of treatment for the difficult problem of severe rectal urgency.

ASGBI: Upper Gastrointestinal 1–9

Friday 27 April 2001 09:15–10:45

UGI 001

Improving outcome in patients with oesophageal cancer: a 25-year audit

H M Sue-Ling, K D Zafirellis, A Fountoulakis, K Dolan,
S P L. Dexter, I G Martin, M J McMahon and D Johnston
*Academic Division of Surgery and Centre for Digestive Diseases,
The General Infirmary, Leeds, UK*

Aims: Major changes to the management of patients with oesophageal cancer have been made in the 1990s, including increased subspecialization, better staging by spiral CT and EUS and greater use of adjuvant radiotherapy and chemotherapy Whether or not these changes have made any difference to clinical outcome is as yet unknown
Methods: A retrospective review of all patients who underwent oesophageal resection in the 1990s was carried out and the results compared with a similar audit of oesophageal resections between 1975 and 1988 that was previously reported (1) from the same institution
Results:

	1975–88	1990–99
Oesophageal resections	106	204
Number of surgeons	17	4
Mortality	27%	12 7%
Morbidity	74%	53 4%
5 years survival	7%	24 1%
Median survival (months)	9 7	18 3

Conclusions: The results of this study are encouraging and suggest that outcome may be improved by concentration of patients in specialised units
Reference: 1. Sagar P M , Gauperaa T , Sue-Ling H *et al* An audit of the treatment of cancer of the oesophagus *Gut* 1994; 941–5

UGI 002

The management of mediastinal leaks following radical subtotal oesophagectomy

P J Lamb, S M Dresner, J Shenfine, D Karat, N Hayes and
S M Griffin
*Northern Oesophago-Gastric Cancer Unit, Royal Victoria Infirmary,
Newcastle Upon Tyne, UK*

Aims: Mediastinal leakage following oesophagectomy is a devastating event carrying a high mortality rate. The aim of this study was to evaluate the incidence, aetiology, management and outcome of mediastinal leaks following two-phase subtotal oesophagectomy with a stapled intrathoracic anastomosis.
Methods: From 1/4/90 to 30/9/00, 291 consecutive patients have undergone radical oesophagectomy with gastric interposition for malignancy in this institution Postoperatively, patients with clinical features suggestive of mediastinal sepsis were investigated with contrast radiography and flexible upper GI endoscopy Of these, 19 patients (6 5 per cent) with a M F ratio of 3 1 and a median age of 64 years had proven mediastinal leakage
Results: The median time to diagnosis was 8 days following surgery (range 3–30) Contrast radiography and endoscopy identified 13 patients with isolated anastomotic leaks and two with widespread leakage secondary to gastrotomy line dehiscence Endoscopy revealed a further four patients with gastric necrosis in whom initial contrast radiography was normal. Patients who developed leaks did not have a significantly higher incidence of cardiorespiratory disease/diabetes ($P = 0\,612$) or smoking ($P = 0\,343$) although intraoperative anastomotic technical difficulties were noted in 26 per cent (5/19) All 13 isolated anastomotic leaks were managed non-operatively with extensive mediastinal drainage, intravenous antibiotics, nasogastric decompression and enteral hyperalimentation with a mortality rate of 15 per cent (2/13) Patients with gastrotomy dehiscence or gastric necrosis had a more severe clinical picture and were managed with repeat thoracotomy and either revision of the conduit or resection and exclusion. Despite early intervention the mortality in this latter group was 67 per cent (4/6) In the 13 patients discharged from hospital the overall 2-year survival rate was 40 per cent with one patient (8 per cent) developing a benign anastomotic stricture
Conclusions: Mediastinal leaks are a relatively infrequent complication of intrathoracic stapled oesophago-gastrostomy and require both contrast radiography and endoscopic evaluation for their accurate detection Isolated anastomotic leaks can be successfully managed with aggressive nonoperative treatment in the majority of cases whereas more extensive leaks from the gastric conduit require revisional surgery carrying a high mortality rate

UGI 003

Prognostic significance of the ratio of invaded to removed lymph nodes in oesophageal cancer

K D. Zafirellis, K. Dolan, A Fountoulakis, S P.L. Dexter and
H M Sue-Ling
*Academic Division of Surgery and Centre for Digestive Diseases,
The General Infirmary, Leeds, UK*

Aims: Prognostic factors that may be influenced by surgical therapeutic measures such as the extent of resection and lymphadenectomy are of particular interest in oesophageal cancer The aim of the present study was to determine prognostic factors in patients with oesophageal cancer undergoing resection with special reference to lymph node metastasis
Methods: From January 1990 to December 1999, 204 patients with oesophageal cancer underwent resection The ratio of adenocarcinomas to squamous cell carcinomas was 3 5.1 The majority (77%) of tumours were located in the lower third of the oesophagus Both univariate and multivariate analysis of prognostic factors were performed
Results: The median age of patients was 66 years (range 29–89) with a male to female ratio of 2 5 1 The overall 5-year survival was 24 1%, with a median survival of 18 3 months. Univariate analysis identified the depth of tumour invasion, nodal involvement, presence of distant metastases, UICC stage, presence of residual tumour (R category), circumferential resection margin involvement, number of involved lymph nodes and ratio of involved lymph nodes to resected lymph nodes as significant ($P < 0\,05$) factors in predicting overall survival. Multivariate analysis demonstrated R category (relative risk 3 4, $P < 0\,01$) and lymph node ratio (relative risk 1 8, $P < 0\,02$) as independent predictors of overall survival. Five-year survival was 37 7% for patients who underwent R0 resection and 0 for R^2 resection The 5-year survival rate of patients without lymph node metastasis was 49 4% compared with 11 4% for patients with nodal metastasis The patients with less that 20% involved lymph nodes fared significantly better than patients with more than 20% involved nodes 23 4% *versus* 7 2% 5-year survival, log rank test = 20.4, 2 d f , $P < 0\,0001$
Conclusions: Radical resection with extended lymphadenectomy may have a role in improving outcome in patients with oesophageal cancer.

UGI 004

The role of antroduodenal dysmotility in gastro-oesophageal reflux disease and Barrett's columnar lined oesophagus

R M Navaratnam, A Watson and M.C. Winslet
*University Department of Surgery, Royal Free Hospital, London
NW3 2QG, UK*

Aims: Antroduodenal dysmotility has been implicated in the pathogenesis of duodeno-gastro-oesophageal reflux (DGOR) and in turn,the role of alkaline bile reflux in GOR and its sequelae is well recognized Non-invasive assessment of antroduodenal motility, utilising electrogastrography (EGG) and antral ultrasound (AS) in GORD is well documented, however, there are no previous comparative studies with Barrett's CLO
Methods: A prospective study group of seven asymptomatic control patients, 15 patients with Barrett's CLO (mean age 60, no evidence of high grade dysplastic changes, four patients with short segment Barrett's CLO) and 30 patients with varying grades of endoscopic oesophagitis (mean age 52, 5 patients with grade IV Savary Millar changes, the remainder had grade I–II changes) was undertaken Each patient underwent initial preprandial EGG and AS analysis, followed by a standardized test meal (500 kcal) and subsequent postprandial EGG and AS analysis for an identical time period
Results: Our results reveal that the mean pre- and post-prandial frequencies for all patient groups fall within normal limits, i e slow wave activity is greater than 70 per cent in all patient groups However, the degree of antroduodenal dysmotility (both pre- and post-prandial values) was more marked in the Barrett's CLO and GORD groups, respectively, in comparison to the control group ($P = 0\,001$) In addition, postprandial frequencies were delayed in the Barrett's CLO group in comparison to the GORD group ($P = 0\,08$) Increased antral diameters were identified in the post-prandial phase in the Barrett's CLO group in comparison to the GORD patients and asymptomatic control group
Conclusions: This study suggests that antroduodenal dysmotility is more marked in a Barrett's CLO patient group in comparison to a GORD and an asymptomatic control group This may partly explain the increase in bile delivery to the distal oesophagus, in Barrett's CLO patients and be associated with their recognized increased morbidity

UGI 005

Persistent acid reflux in asymptomatic patients with Barrett's oesophagus on medical therapy: a case for fundoplication

A.I. Sarela, D.G. Hick[1], J.F. Casey[1], D.S. O'Riordain, P.J. Guillou and G.W.B. Clark

Professorial Surgical Unit and [1]Department of Clinical Sciences & Research, University of Leeds, St James's University Hospital, Leeds, UK

Aims: In patients with long-segment Barrett's oesophagus (LSBE), relief from reflux symptoms is used as the clinical endpoint for proton pump inhibitor (PPI) therapy. This study aimed to determine: (1) whether this endpoint is appropriate for normalization of intraoesophageal pH; and (2) the prevalence of bile reflux in patients with LSBE.

Methods: Station pull-through manometry and 24-h ambulatory oesophageal pH monitoring were performed on 27 patients with LSBE who had been rendered asymptomatic on PPI therapy. Oesophageal bile reflux was measured spectrophotometrically using Bilitec 2000, prior to PPI therapy [values as median (interquartile range)].

Results: Patients comprised 23 men and four women of median age 64 years, with 6 (4–9) cm of LSBE and a lower oesophageal sphincter pressure (LOSP) of 6.5 (5–10) mmHg, receiving either omeprazole ($n=17$; 40 mg daily) or lansoprazole ($n=10$; 30 mg daily). Twelve (44 per cent; Group A) patients showed persistent pathological acid reflux on therapy, while 15 (56 per cent; Group B) patients exhibited normalization of acid reflux (table). Further, although pathological bile reflux was evident in both groups, abnormalities were clearly pronounced in Group A (table).

	Group A	Group B
% total time pH < 4	16.9 (6.7–19.7)	1.2 (0.4–2.2)
% supine time pH < 4	15.6 (7.9–38.8)	0 (0–2.0)
% erect time pH < 4	8.8 (2.6–21.5)	1.0 (0.3–2.2)
% total time absorb. ≥0.14	22.4 (4.0–34.0)	9.4 (0.2–40.9)
% supine time absorb. ≥0.14	16.8 (3.9–57.4)	4.4 (0.5–82.1)
% erect time absorb. ≥0.14	17.8 (0.7–36.9)	0.9 (0–12.8)

The two groups were similar for age, gender, PPI therapy, presence of hiatus hernia, length of LSBE or LOSP.

Conclusions: Up to one-half of patients with LSBE, who are asymptomatic on PPI therapy, exhibit persistent pathological acid reflux and commonly have increased bile reflux as well as a defective LOS. A fundoplication operation needs to be considered when pH monitoring indicates failure to eradicate pathological reflux.

UGI 006

Division of short gastric vessels at laparoscopic Nissen fundoplication: a prospective double-blind randomized trial with 5-year follow-up

C.J. O'Boyle, D.I. Watson, J.C. Myers, P.G. Devitt, P.A. Game and G.G. Jamieson

Royal Adelaide Centre for Endoscopic Surgery and Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia

Aims: Whether or not short gastric vessel (SGV) division should be undertaken at laparoscopic Nissen fundoplication (LN) is still controversial. The aim of this study is to establish whether division of SGV confers clinical benefit at 5 years following surgery for gastro-oesophageal reflux disease.

Methods: Between May 1994 and October 1995 one hundred and two patients underwent LN. By September 2000 99 (50 no division, 49 division) patients were available for follow-up and were submitted to a detailed telephone interview by an independent investigator.

Results: There was no significant intragroup difference in the incidence of epigastric pain, regurgitation, odynophagia, early satiety, inability to belch, anorexia, nausea, vomiting, nocturnal coughing and wheezing. There was no difference in the incidence of heartburn when estimated empirically (18 per cent *versus* 12 per cent, $P=0.42$) or by visual analogue scale (Mean 1.1 *versus* 1.0, $P=0.88$) and no difference in the incidence of dysphagia when estimated empirically (36 per cent *versus* 31 per cent, $P=0.57$), by visual analogue scale (2.2 *versus* 2.8, $P=0.35$), or by composite dysphagia score (8.9 *versus* 10, $P=0.53$) between no division and division of SGV, respectively. There was a significant increased incidence of flatus production (88 per cent *versus* 70 per cent, $P<0.04$) epigastric bloating (71 per cent *versus* 48 per cent, $P<0.02$) and a decreased incidence of ability to relieve bloating (39 per cent *versus* 60 per cent, $P<0.04$) in patients who underwent division of the SGV.

Conclusions: Division of the SGV during laparoscopic fundoplication does not improve any measured clinical outcome and leads to an increase in 'wind-related' symptoms.

UGI 007

The role of antioxidant vitamins in the progression of Barrett's oesophagus to adenocarcinoma

A. Fountoulakis, I.G. Martin,[1] K. White,[2] L.J. Hardie,[2] H.M. Sue-Ling[1] and C.P. Wild[2]

[1]Academic Division of Surgery and [2]Molecular Epidemiology Unit, Epidemiology and Health Services Research, School of Medicine, University of Leeds, UK

Aims: The sharp increase in the incidence of oesophageal adenocarcinoma over a relatively short period of time indicates that environmental factors are involved in the aetiology and epidemiological data suggest that dietary antioxidants might have a protective effect against the development of the disease. The aim of this study was to measure tissue and plasma levels of vitamin C and ascorbic acid in patients with Barrett's oesophagus.

Methods: Blood samples and endoscopic biopsies from squamous, Barrett's, and gastric mucosa were obtained from consecutive patients participating in a surveillance programme. Vitamin levels were measured by high performance liquid chromatography and mean values were compared by a two-tailed unpaired t-test.

Results: Forty-two male and 15 female volunteers were recruited. Histology of the Barrett's epithelium revealed nine cases with gastric metaplasia, 45 with intestinal metaplasia and three with dysplasia. The mean values ± SD) of ascorbic acid in squamous, Barrett's and gastric mucosa were 111.1 (±51.1), 86.9 (±38) and 75.8 (±35.8) $\mu g\ g^{-1}$, respectively. The difference between the mean values in squamous and Barrett's mucosa was statistically significant ($P=0.02$). The difference between Barrett's and gastric mucosa was not significant. There was also a statistically significant difference between the mean plasma levels of ascorbic acid in male [mean = 7.51 (±3.7) $\mu g\ mL^{-1}$] and female [mean = 10.14 (±4.2) $\mu g\ mL^{-1}$ patients ($P=0.04$). A trend towards a decrease in the mean plasma levels of ascorbic acid was noted between patients with gastric metaplasia, intestinal metaplasia and dysplasia (10.57 *versus* 7.98 *versus* 4.56 $\mu g\ mL^{-1}$) but this failed to reach statistical significance due to the small number of patients in each subgroup. Similar results were obtained for the tissue and plasma levels of vitamin C.

Conclusions: These results suggest that oxidative mechanisms might play an important role in determining which patients with Barrett's oesophagus will progress from metaplasia to dysplasia and adenocarcinoma perhaps by modulating DNA damage in oesophageal mucosa.

UGI 008

Endoscopic ablation of Barrett's oesophagus by argon beam plasma coagulation: long-term follow-up

C.D. Morris, J.P. Byrne and S.E.A. Attwood

Department of Gastro-Oesophageal Surgery, Hope Hospital, Manchester, UK

The incidence of oesophageal adenocarcinoma has risen dramatically over the last 30 years. Patients with Barrett's oesophagus have a risk of approximately 1 : 100 patient years for the development of this tumour. Endoscopic ablation of Barrett's oesophagus has been shown to lead to the regrowth of a 'neo' squamous epithelium if gastro-oesophageal reflux is controlled, but the incidence of subsequent tumour formation is unknown. Here we report the long-term follow up of 49 patients who have undergone endoscopic ablation of Barrett's oesophagus by argon beam plasma coagulation (ABPC).

Patients: Of the cohort, nine had low-grade dysplasia (LGD), nine had high-grade dysplasia (HGD) with the remainder having nondysplastic Barrett's metaplasia. The mean length of Barrett's segment was 6.7 cm (range 3–16 cm). 10 patients had reflux control by antireflux surgery with the remainder receiving high-dose proton-pump inhibitor therapy.

Ablation: ABPC was applied in longitudinal strips with mucosal bridges left between strips. These were ablated at further sessions. All metaplasia were ablated to within 3 cm of the gastro-oesophageal junction. All procedures were carried out as day-case procedures under intravenous sedation.

Follow-up: To date, one patient has died of unrelated disease but the remaining patients have been followed by regular endoscopic surveillance for a mean of over 3 years to give a total follow up of 141.4 patient years. No malignancy has developed in any patient during follow-up, including those with initial dysplasia.

Conclusions: This cohort represents the largest reported follow-up after prophylactic ablation of long-segment Barrett's oesophagus The absence of malignant complications strengthens the argument for endoscopic ablation in the prevention of oesophageal adenocarcinoma

UGI 009

Surgical resection for high grade dysplasia arising in Barrett's oesophagus

S M Dresner, P J Lamb, D Karat, N. Hayes, S A Raimes and
S M Griffin

*Northern Oesophago-Gastric Cancer Unit, Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP, UK*

Aims: The role of surgery in the management of patients with high-grade dysplasia (HGD) arising within Barrett's mucosa remains controversial The aim of this study was to determine the incidence of invasive adenocarcinoma (ACA) in patients undergoing oesophagectomy with a preoperative endoscopic biopsy diagnosis of HGD

Methods: Between 1/4/90 and 1/11/00 a consecutive series of 25 patients with a preoperative histological diagnosis of HGD arising in Barrett's oesophagus have undergone radical two-phase oesophagectomy All patients underwent at least two endoscopic assessments and systematic biopsy with histological interpretation of material by two experienced pathologists. Clinicopathological data from this cohort of patients were compared with a meta-analysis of published results of surgery for HGD in Barrett's oesophagus from 1990 to 2000

Results: The male to female ration was 7 1 and the median age 62 years (range 45–75). All patients had endoscopic evidence of macroscopic lesions within their Barrett's segments comprising irregular mucosa ($n = 10$), raised nodular or polypoid lesions ($n = 10$), depressed ulceration ($n = 4$) and stricture ($n = 1$) Surgical approach and resection techniques were the same in all patients Major complications occurred in 24 per cent including one chyle leak and an intrathoracic bleed both requiring re-operation. The 30-day and in-hospital mortality rate was 4 per cent Final histopathological assessment of resected specimens demonstrated 11 patients with invasive ACA representing an underlying malignancy rate of 44 per cent Invasive tumours were limited to the mucosa in seven cases, submucosa in three cases, and muscularis propria in one case with all specimens demonstrating areas of adjacent multifocal HGD No patients had nodal metastases Overall 1-year and 5-year survival rates were 96 per cent and 85 per cent, respectively A meta-analysis of the published results of 213 patients undergoing resection over the last 10 years demonstrated an operative mortality rate of 2 per cent, an incidence of invasive carcinoma of 44 per cent and a 5-year survival rate >85 per cent

Conclusions: A substantial percentage of patients with HGD arising in Barrett's mucosa have invasive carcinoma at the time of diagnosis which is not detectable by endoscopic biopsy Resection carries a low operative risk, achieves an excellent long-term outcome and should remain the standard therapy for Barrett's esophagus with HGD.

ASGBI: Colorectal 16–20 — Friday 27 April 2001 11:15–12:15

Colorectal 016

The use of PET for the evaluation of recurrent or metastatic colorectal cancer

T.H.A. Arulampalam,[1] D.C. Costa,[1] M. Loizidou,[1] P.B. Boulos,[1]
P.J. Ell[2] and I. Taylor[1]
[1]Department of Surgery & [2]Institute of Nuclear Medicine, Royal Free and University College Medical School, London, UK

Aims: Positron emission tomography (PET), a noninvasive, functional imaging modality is a limited resource in the UK whose place in colorectal cancer (CRC) management needs to be evaluated against advanced, conventional cross-sectional imaging techniques. This study aims to compare PET with spiral computed tomography (CT) for the detection of recurrent/metastatic CRC, assessment of spread and evaluation of the degree to which clinical management is altered.

Methods: Forty-two patients who were referred for either detection and/or staging of recurrent CRC were prospectively recruited to undergo whole body PET and CT. Results of PET and CT, verified by clinical and radiological follow up and/or biopsy, were compared to establish which imaging modality was most accurate for detecting recurrence and assessing spread.

Results: PET (sensitivity 93.5 per cent, specificity 63.6 per cent) was more accurate than CT (sensitivity 71.0 per cent, specificity 72.7 per cent) for detecting recurrence in the 21 patients assessed for this reason. PET (sensitivity 100 per cent, specificity 100 per cent) was also more accurate than CT (sensitivity 55.0 per cent, specificity 100 per cent) for assessing extent of spread and in total resulted in a change in clinical management in 16 patients (38.1 per cent).

Conclusion: This study demonstrates that PET is more accurate than CT for the evaluation of patients with suspected or confirmed recurrent/metastatic CRC. As a result of these findings PET led to a change in clinical management which included avoiding surgery in patients with disseminated disease and prompt commencement of alternative treatments.

Colorectal 017

Plasma big endothelin – a tumour marker in localized and metastatic colorectal cancer

C. Arun, K.E. Porter, N.J.M. London and D.M. Hemingway
University Department of Leicester, University of Leicester, UK

Aims: Changes in liver blood flow caused by an unknown splanchnic vasoconstrictor have been noted in colorectal cancer patients with liver metastases. This prospective study was performed to assess whether plasma levels of big endothelin-1 (big ET-1), stable precursor of the most potent vasoconstrictor (endothelin –1), were associated with liver metastases in colorectal cancer.

Methods: Plasma samples of patients who underwent surgery for primary colorectal cancer and those with colorectal liver metastases from September 1999 – September 2000 were taken prior to treatment and were compared to age-sex matched controls. Plasma samples thus taken were analysed within 3 months by using single-step sandwich enzyme immunassay (Biomedica, Austria).

Results: Plasma big ET-1 levels in patients with liver metastases ($n=43$) were significantly elevated [4.23 pg mL^{-1} (median)] compared to controls ($n=20$) [2.07 pg mL^{-1} (median)] $P=0.001$ (Mann–Whitney). Median plasma big ET-1 levels in patients with no evidence of liver metastases (2.78 pg mL^{-1}) ($n=37$) were not significantly elevated compared to controls but were significantly lower than colorectal cancer patients with liver metastases [$P=0.003$ (Mann–Whitney)].

Conclusion: This study has demonstrated that big ET-1 could be involved in the spread of colorectal cancer to liver and could be the cause of splanchnic vasoconstriction seen in colorectal cancer patients with liver metastases. Plasma big ET-1 levels in colorectal cancer patients might be useful as a tumour marker for the identification of liver metastases at an earlier stage.

Colorectal 018

Hyaluronan inhibits the adherence of a colon adenocarcinoma cell line, SW1222, to the mesothelium *in vitro*

P. Ziprin, P. Ridgway, D. Peck and A. Darzi
Imperial College School of Medicine, St Mary's Hospital, London, UK

Aims: Approximately 25 per cent of patients who develop recurrent colorectal cancer will present with localized peritoneal metastases. The aim of this study is to investigate the effect of hyaluronan on tumour cell adhesion to the peritoneal mesothelium.

Methods: The adherence of a human colon adenocarcinoma cell line, SW1222, to a monolayer of a primary culture of human peritoneal mesothelial cells was assessed in the presence of hyaluronan or an inhibitory antibody to its ligand, CD44 and compared to control. The percentage of adhered cells was measured after a 30 min incubation period using a fluorometric assay.

Results:

Percentage	Adhesion
Hyaluronan	11.33 ± 2.31#
Anti CD44 Antibody	39.69 ± 4.64
Control	41.69 ± 5.50

# $P<0.001$ hyaluronan *versus* control.

Conclusion: Hyaluronan significantly inhibits tumour-mesothelial cell adhesion, but not through its interaction with the ligand, CD44. This may lead to a potential therapeutic role for hyaluronan in the surgical management of colon cancer.

Colorectal 019

Laparoscopic abdomino-perineal (AP) resection of the rectum for cancer does not confer any disadvantage to long-term survival compared with open AP resection

R.P. Baker, P. Neary, E. White, G.S. Duthie, P.W.R. Lee and J.R.T. Monson
Academic Surgical Unit, Castle Hill Hospital, Hull, UK

Aims: Our aim was to look at long-term survival data in two age- and pathological stage-matched groups of patients who had undergone open or laparoscopic AP resection during a similar time-period and compare their long-term survival outcomes.

Methods: We retrospectively reviewed 93 patients who had undergone AP resections. 24 of these were done laparoscopically, 69 open. Survival data was analysed using Kaplan–Meier survival curves comparing time from operation to date of death or latest hospital contact, if still alive, as significant events for analysis.

Results:

	Laparoscopic AP resection	Open AP resection
Number	24	69
Mean age	63.0	65.2
Stage: Dukes A	3 (12.5%)	8 (11.5%)
Dukes B	8 (33.3%)	24 (34.7%)
Dukes C	13 (54.1%)	36 (52.2%)
Mean survival time (months)	54.48 (range 0–89)	44.40 (range 0–67)

($P=0.155$ log rank).

Conclusion: Laparoscopic AP resection for rectal cancer does not confer any long-term survival disadvantage over open surgery and permits rectal cancer resection without a large abdominal wound.

Colorectal 020

Immune activation in advanced bowel cancer is associated with tryptophan depletion and reduced quality of life

A. Huang,[1] D. Fuchs,[2] B. Widner,[2] G. Tsavellas,[1] D.C. Henderson[3] and T.G. Allen-Mersh[1]
Departments of [1]Surgery and [3]Immunology, ICSM, Chelsea & Westminster Hospital, London. Institute for Medical Chemistry, UK and Department of [2]Biochemistry, University of Innsbruck, Austria

Aims: Immune activation in advanced colorectal cancer is associated with impaired quality of life. We hypothesized that increased immune activation leads to tryptophan depletion, and hence reduced availability of the neurotransmitter serotonin resulting in depression and fatigue.

Methods: Patients with metachronous colorectal liver metastases who had not received chemotherapy completed quality of life (QoL) questionnaires and had blood sampling for the measurement of serum interleukin-2 soluble receptor α (IL-2 sRα, soluble tumour necrosis factor receptor I (sTNF RI), interleukin 6 (IL-6), C-reactive protein (CRP) and tryptophan. Liver metastasis volume was measured by computed tomography

Results: Twenty-five patients (median age 62 years, 17 males, median survival from blood sampling 233 days, median liver metastasis volume 235 mL) were studied. Serum CRP correlated with liver metastasis volume ($r = 0.4$, $P = 0.01$), survival ($r = -0.46$, $P = 0.05$) and all QoL instruments ($P < 0.05$) Serum tryptophan correlated with IL-2 sRα ($r = -0.35$, $P = 0.03$) and sTNF RI ($r = -0.36$, $P = 0.02$), and with QoL (sickness impact profile $r = -0.41$, $P = 0.01$ and physical symptom scores $r = -0.33$, $P = 0.04$)

Conclusion: Immune activation increased with extent of disease and was associated with reduced QoL, tryptophan depletion correlated with this chronic immune response and with QoL deterioration. Reducing tryptophan depletion or increasing serotonin availability may sustain quality of life in patients with advanced colorectal cancer

---

Colorectal 021

Stage IV colorectal cancer with a minimally symptomatic primary tumour: is operation necessary?

A I. Sarela, A. Guthrie,[1] M T. Seymour,[2] N S Ambrose, J. Spencer,[1] P.J. Guillou, and D S O'Riordain

Academic Units of Surgery and Medical Oncology and the Department of [1]Radiology, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK

Aims: For patients with primary colorectal cancer (CRC) and unresectable synchronous metastases, operations to prevent complications are associated with substantial morbidity and delay in the initiation of chemotherapy We studied if operation could be safely avoided in a select group with minimally symptomatic primary tumours.

Methods: Patients with clearly incurable stage IV CRC, in whom immediate excision of the primary tumour was unnecessary for satisfactory palliation, were identified during 1997–2000. Those unfit for either surgery or chemotherapy were excluded. Dual-contrast spiral computerised tomography (CT) scans were reviewed in detail. Careful clinical follow-up for tumour-specific complications was conducted

Results: There were 10 men and 10 women of median age 70 years Main presenting symptoms were change bowel habits (eight), rectal bleeding (five), weight loss (four), dysuria (two), or appendicitis (one) Primary tumours were located in the right colon (five), transverse colon (one), left colon (seven) and rectum (seven). Liver metastases were noted in 19 patients and replaced <25 per cent of the liver in 8, 25–50 per cent in 5 and >50 per cent in six patients. Lung metastases were noted in seven and ascites or peritoneal deposits in four patients There was no evidence of intestinal obstruction on the baseline CT scan in any case. Following diagnosis, all patients received systemic 5-FU-based chemotherapy. At median follow-up of 12 months, the 1-year actuarial survival rate was 53 per cent Three patients with sigmoid cancers developed colonic obstruction requiring uncomplicated bowel resection in one and insertion of a colonic stent in two patients, at intervals of 3, 12 and 20 months from diagnosis

Conclusion: Resection of a minimally symptomatic primary tumour may be safely deferred in patients with good performance status who receive systemic chemotherapy Such a policy is associated with a low risk of complications prior to death due to progressive systemic disease.

ASGBI: Hepatobiliary 1–12 Friday 27 April 2001 14:00–16:00

HPB 001

Long-term results of distal pancreatectomy for chronic pancreatitis

R.R. Hutchins, R.S. Hart, M. Pacifico and R.C.N. Williamson

Hammersmith Hospital, DuCane Road, London W12 0HS, UK

Aims: To determine the long-term results of distal pancreatectomy for chronic pancreatitis in terms of survival, pain relief and pancreatic function.
Methods: Among 75 patients with chronic pancreatitis operated over a 20-year period, there were 50 men and 25 women of median age 41 year (range 17–75 year). Aetiological factors were alcoholism ($n=42$), miscellaneous ($n=8$) or unknown ($n=25$). Median duration of symptoms was 36 month (range 1–300 months). The dominant symptom was pain ($n=69$); eight had acute on chronic pancreatitis, 30 patients had pseudocyst, 5five bleeding/pseudoaneurysm and three suspicion of cancer. There was endocrine dysfunction in 17 and exocrine dysfunction in 31.
Results: Distal pancreatectomy was completed in a median 3.5 h (range 1.5–6.5 h) with conservation of the spleen in 27 of 75 cases (36 per cent). The postoperative morbidity rate of 31 per cent was not affected by splenectomy; four patients were re-operated on for bleeding or fistula. There was one early postoperative death from haemorrhage, another death within 12 months from pulmonary embolus and seven late deaths, giving an overall mortality rate of 12 per cent. Two late deaths were due to pancreatic disease (pancreatitis, diabetes) and five to continuing alcoholism (suicide, cardiomyopathy, cirrhosis, bleeding duodenal ulcer, pneumonia). At a median follow-up of 38 month (range 2–247 month), 32 of 69 patients were pain-free, six had mild/occasional pain and 31 had troublesome pain, of whom 23 underwent further intervention (operative or radiological neurolysis $n=9$, completion pancreatectomy $n=12$, sphincteroplasty $n=1$ and cystojejunostomy $n=1$). Repeat glucose tolerance curves were diabetic in 31, impaired in eight and normal in 30, while exocrine failure was detected in 42 patients.
Conclusion: Distal pancreatectomy achieves long-term analgesia in 50 per cent of cases and marked improvement in another 5 per cent at the expense of some initial risk (1.3 per cent operative mortality rate) and a tendency to exacerbate diabetes far more than exocrine disturbance. Three-quarters of those with recurrent pain may require further treatment, whether neurolytic or resectional.

HPB 002

A prospective randomized controlled trial comparing nasogastric and nasojejunal feeding in severe acute pancreatitis

F.C. Eatock, P. Chong, N. Menezes, C.W. Imrie, C.J. McKay and C.R. Carter

Lister Department of Pancreatico-biliary Surgery, Glasgow Royal Infirmary, UK

Aims: Enteral feeding is now the preferred methods of nutritional support in patients with severe acute pancreatitis, however, the placement of nasojejunal tubes by X-ray screening or fibreoptic endoscopy can be problematical. We have previously reported pilot date suggesting nasogastric feeding severe acute pancreatitis may be practical and safe. We undertook a randomized controlled trial comparing feeding via nasogastric and nasojejunal routes in patients with severe acute pancreatitis.
Methods: Fifty patients admitted with severe acute pancreatitis were randomized to receive either nasogastric or nasojejunal feeding. Severity of disease was defined by Glasgow Prognostic Criteria, APACHE II Score, CRP and contrast-enhanced CT scan. All patients received full supportive care with cardio-ventilatory and renal support as required. CRP and pain were assessed daily (Memorial Sloan-Kettering linear analogue scale).
Results: Aetiology was identified as gallstones (29 patients), ethanol (18) and miscellaneous (three). Four patients died in each group. There was no significant differences between study groups. The table shows mean CRP levels (+ standard error (SE)) and mean pain scores (SE) on the first 5 days of feeding:

	Day 1	Day 2	Day 3	Day 4	Day 5
NG group CRP	249	210	170	129	99
	(30.7)	(46.5)	(36)	(21)	(18)
NJ group CRP	211	175	174	117	100
	(32.1)	(33.1)	(36)	(44)	(29)
NG group pain	6.5	5.7	2.9	4.9	0.5
	(1.2)	(1.1)	(2.3)	(2.6)	(0.1)

Conclusion: We conclude that there is no clinically apparent adverse effect from nasogastric feeding in severe acute pancreatitis and avoids the logistical problems associated with nasojejunal route.

HPB 003

ERCP or MRCP – clinical pathway based on 1000 consecutive cases

R. Dawson, L. Moseley,[1] M.E. Foster and E. Hicks

Royal Glamorgan Hospital, Llantrisant, Mid Glamorgan, [1]University of Glamorgan, School of Care Sciences, UK

Aims: The aim of this study is to define the optimal role of magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) in assessing biliary and pancreatic disease.
Methods: The records of 1000 patients who underwent ERCP were reviewed from the departmental register. Data were gathered about the clinical indications for the procedure, ultrasound findings, liver function tests and the outcome of ERCP. Patients were placed in one of 14 indication groups. These data were analysed to obtain a therapeutic rate (proportion of therapeutic examinations) for each group. A projection was then made on these 1000 patients by allocating those with a therapeutic rate (TR) >60 per cent to an ERCP in the first instance and those with TR <60 per cent to a MRCP. The number of projected normal ERCPs and dual imaging avoided was calculated.
Results: One thousand attempted ERCPs were reviewed of which 911 were successful (91 per cent). The 'therapeutic rate' of ERCP varied according to the indications. In patients with jaundice and dilated ducts it was 80 per cent, while in patients with abdominal pain and abnormal liver function tests (LFTs) or jaundice the TR was 22 per cent. The odds were more evenly matched in pain and dilated ducts (41 per cent), pancreatitis with abnormal LFT's or dilated ducts (46 per cent) and abnormal LFTs alone (39 per cent). Other therapeutic rates include postoperative bile leak (95 per cent), RUQ pain only (17 per cent), jaundice alone (65 per cent), dilated ducts alone (70 per cent), and pancreatic mass (98 per cent). Using a 60 per cent TR cut-off projection, 305 ERCPs would have been avoided completely in this group although 77 normal examinations would have been performed. Only 131 patients would have had both MRCP and ERCP. These results are significant (chi square $=350.2$, df $=26$, $P<0.01$). They are also clinically important with an eta (outcome as dependent) of 0.398.
Conclusion: Patients who fall in indication groups with a therapeutic rate >60 per cent should have an ERCP in the first instance and those with TR <60 per cent should have a MRCP. This will result in fewer nontherapeutic ERCPs but at the same time, less dual imaging and better utilization of resources.

HPB 004

Surgical bypass *versus* non-surgical palliation for unresectable pancreatic head and periampullary malignancy

A.G.W. Moses, A.R. Davies, N. Dowidar, K.K. Madhavan, J.F. Forbes,[1] R.W. Parks and O.J. Garden

Departments of Clinical and Surgical Sciences (Surgery), and [1]Public Health Sciences, University of Edinburgh, UK

Aims: Those surgeons who dispute the value of laparoscopy, laparoscopic ultrasound or endoscopic ultrasound in the staging of potentially resectable pancreatic head and periampullary malignancies claim the patient diagnosed with unresectable cancer (without metastases on a CT scan) would be best palliated by a prophylactic surgical biliary and gastric bypass procedure; despite the absence and the unlikelihood of there ever being an appropriate prospective randomized trial to address this question in the era of CT imaging. We have performed the closest appropriate study, comparing patients staged grade II (sII) at laparoscopic ultrasound (and thus not receiving a primary operation) with those staged as grade I who subsequently received a surgical bypass (SB) due to unresectable disease, in order to determine whether surgical bypass offers potential benefit (accepting the potential bias in this study in favour of the bypassed group).
Methods: Theatre records and the Lothian Surgical Audit Database were used to identify 92 appropriate patients who had undergone laparoscopic staging with a view to potential pancreaticoduodenectomy between Jan 1995 and May 2000. 21 of these patients had been staged as having low volume grade IV disease (sIV) at laparoscopy, but they were included in this study as we were interested to compare their outcome with the stage II patients. District hospital (if appropriate), Edinburgh Royal Infirmary and primary

care case notes for the patients were obtained following death and reviewed for data collection A complete record of survival from and all procedures occurring following the date of laparoscopic ultrasound until death was therefore obtained without the potential bias of over intervention which may occur in a prospective study (Data expressed· median with range, comparisons between groups were made using Mann–Whitney U-test)

Results: Thirty-five patients underwent a surgical bypass (SB), 36 and 21 underwent non surgical palliation for stage II (sII) and stage IV (sIV) disease, respectively There was no significant difference in survival (months) assessed by the Kaplan–Meier method between the three groups (SB 6 8, 1 5–32 7; sII 7 6, 0 9–19 61, sIV 6 3, 1 0–32 4) Total days spent in hospital was significantly greater for bypassed patients (SB 26, 13–74, sII 15, 1–64, sIV 13, 2–33), SB *versus* $P = 0\ 0045$, SB *versus* sIV $P < 0\ 0001$ 10 out of 57 patients treated non-surgically had never been jaundiced (despite lesions in the head and uncinate) and were not stented, while 23 subsequently required further stenting (11 patients requiring one, and eight requiring two subsequent stents) Nine patients experienced late gastric outlet obstruction (sII 5, sIV 4) (at 5, 0 7–18 months), although one in each group did so at a terminal stage of their illness the rate of late gastroenterostomy being 12 per cent The supposition that surgical bypass reduced subsequent hospitalizations (SHo) was not supported SB post bypass (SHo events *1*, 0–12· days 9, 0–53), sII post laparoscopy (SHo events 1, 0-8 days 12, 0–64), sIV (SHo events 2, 0-3 days 10, 0–32) There was also no difference in hospice utilization

Conclusion: As patients undergoing surgical bypass procedures spend significantly more days in hospital yet have no improvement in survival or subsequent hospitalizations, inappropriate laparotomy can be avoided by the use of staging laparoscopy and laparoscopic ultrasonography Patients staged as grade IV at laparoscopy have a similar outcome to those with only locally unresectable disease.

HPB 005

Management of choledochal cysts in adults

H.D Atkinson, C P Fischer, K de Jong, K K Madhavan, R.W Parks and O.J Garden

University Department of Surgery, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

Aims: Choledochal cysts are rare in the western world and are diagnosed primarily in childhood The management of these lesions in adults is complex, as many patients undergo inadequate operations as children We present a contemporary cohort of patients that emphasizes the complexity of management of this disorder in adults.

Methods: The medical records of all adults presenting with choledochal cysts to Edinburgh Royal Infirmary, between 1992 and 2000 were reviewed Detailed analyses were made of their clinical presentations, biochemical and radiological findings, management, anatomical anomalies, complications and outcomes

Results: Seventeen patients (13 females and four males) with a mean age of 28 years (range 18–49) were identified. According to the Todani classification of congenital bile duct cysts, 13 patients had Type I cysts, two had Type IVa cysts, one had a Type V cyst, and one had a Type IVa/V cyst. All patients had recurrent abdominal pain, 80 per cent with symptoms of recurrent nausea, 53 per cent with vomiting, 20 per cent with dyspepsia and 13 per cent with weight loss At referral, 60 per cent of patients had a history of cholangitis and 27 per cent had a previous episode of pancreatitis Delay to diagnosis (symptom onset to referral) ranged from 1 week to 6 years (mean 11 months) A number of anomalies were identified during investigation or at operation, including aberrant hepatic artery (24 per cent), anomalous p–b junction (18 per cent), accessory gallbladder (6 per cent) and primary ductal stricture (6 per cent) Eight of the 17 patients had previous biliary surgery as children or young adults Cholecystectomy had been performed in two patients, cystduodenostomy in five patients while a further patient had undergone transduodenal sphincteroplasty for recurrent pancreatitis The cyst (or part of the cyst) remained *in situ* in all patients who had undergone previous surgery 16 patients underwent definitive surgery at our institution, which included complete cyst excision and hepaticojejunostomy while one patient is awaiting liver transplant There were no operative deaths and no cases of malignancy were found Four of the 16 patients had minor postoperative complications Two patients required additional revision of the hepatico-jejunostomy for recurrent cholangitis

Conclusion: Many adults with choledochal cysts have undergone a previous inadequate operation, which increases the complexity of subsequent surgical procedures Complete cyst excision with hepaticojejunostomy is the recommended therapy for patients with choledochal cysts. Patients with choledochal cysts who have undergone previous operative procedures in which the cyst has been incompletely excised, should undergo definitive revisional surgery

HPB 006

Day surgery laparoscopic cholecystectomy with a 6-hour stay as a successful routine procedure

R A Coulthard and J J T Tate

Department of Surgery, Royal United Hospital, Bath, UK

Aims: To introduce laparoscopic cholecystectomy to our Day Surgery Unit and assess the implications of a 6-h post op stay

Methods: All patients with symptomatic gallstones were considered for day-case laparoscopic cholecystectomy Patients were excluded if major medical comorbidity but not on the basis of age or BMI Surgery was performed in a dedicated Day Surgery Unit and cholangiography was performed selectively All patients were assessed at 6 h post operatively for discharge and followed up by telephone at 24 h, 48 h and 2 weeks post op

Results: One hundred and thirty-two patients (114 female (86 per cent), 18 male) were studied, 90 patients (69 per cent) were discharged at 6 h Of these one patient (1 1 per cent) required a GP visit at home within 24 h and 1 patient required readmission through A & E The remaining 88 patients (97.7 per cent) reported no problems and were satisfied with day-case treatment Two patients subsequently required admission (ileus one, bile leak one), but no-one required further surgical intervention Of 40 patients admitted two required open surgery (1 5 per cent), the remaining patients were complaining of nausea or drowsiness in approximately equal proportions

Conclusion: Day-case laparoscopic cholecystectomy is successful in the majority of patients, if a significant number of overnight admissions is anticipated

HPB 007

An unusual experience of laparoscopic bile duct exploration

S E Tranter and M H Thompson

Department of Surgery, Southmead Hospital, Bristol

Aims: Most reports of laparoscopic bile duct exploration suggest that a relatively high proportion of stones can be removed via the cystic duct with success rates around 90 per cent Conversion to open exploration is usually well below 10 per cent

Methods: One hundred and thirty-eight patients aged 17–90 (mean 550) have undergone laparoscopic exploration of the common bile duct. 46 per cent were jaundiced at the time of operation Transcystic exploration was attempted in all but only achieved in 37 (27 per cent) The ability to perform transcystic exploration related more to the configuration of the cystic duct than to stone size Initial duct clearance failed in 18 per cent because of impacted stones This was reduced to 2 per cent after lithotripsy was introduced for impacted stones

Results: Conversion for severe gallbladder inflammation occurred in 11 per cent of cases 60 per cent of these patients were jaundiced at the time of the operation but they did not have larger stones There were no deaths and no pancreatitis complications occurred in 17 per cent Median postoperative stay was 2 days for transcystic and 4 days for transductal exploration

Conclusion: Laparoscopic bile duct exploration effectively clears the bile duct a high transductal rate and conversion rate for gallbladder inflammation have been observed

HPB 008

A ten-year experience in the management of gallbladder cancer

G C S Smith, J. Burns, K.K. Madhavan, O J Garden and R W. Parks

Department of Hepatobiliary Surgery, The Royal Infirmary of Edinburgh, Edinburgh, UK

Aims: To assess outcome in all patients diagnosed with gallbladder cancer within a tertiary referral centre over a 10-year period by retrospective case note review

Methods: Patients diagnosed with gallbladder cancer from 1990 to 1999 were identified by review of case notes and pathology records

Results: Fifty-one cases of gallbladder cancer were identified The records of seven patients were unavailable and of the remaining 44 patients, 11 were male and 33 female The mean age at diagnosis was 66 years (range 42–90) Diagnosis was established preoperatively in 25 patients (57 per cent), at cholecystectomy in five patients (11 per cent) and incidentally following pathological examination in 14 patients (32 per cent) Of those diagnosed preoperatively, all 25 were either unresectable or were considered unsuitable for surgery for other reasons. The mean survival in this group was 5 months, however, one patient with T_4 N_0 M_0 remains alive at 30 months. All five patients diagnosed at cholecystectomy were unsuitable for curative resection. The mean survival in this group was 5.5 months. Of the 14 patients with an incidental diagnosis, 8 (57 per cent) had potentially curable disease. Five of these patients underwent hepatic resection and are currently alive or have a postoperative survival of more than 5 years. The other three patients, who all had T1 disease, had no further surgical intervention; one patient remains alive after 8 years and two patients died at 39 and 13 months, respectively. Six patients with an incidental diagnosis of gallbladder cancer had advanced disease or were deemed unsuitable for radical surgery. The mean survival in this group was 10 months.

Conclusion: Prognosis for gallbladder cancer is poor for patients diagnosed preoperatively or at the time of cholecystectomy. The outlook for patients with an incidental finding of gallbladder cancer on pathological assessment is favourable if radical resection is undertaken.

HPB 009

A comparison of standard and extended hepatic resections: indications, complications and outcomes

G.D. Stewart, P.C. Shrestha, E. Currie, K.K. Madhavan, R.W. Parks and O.J. Garden

University Department of Surgery, Royal Infirmary, Edinburgh, EH3 9YW, UK

Aims: This study compares and contrasts the demographics, indications, morbidity, mortality and survival for standard and extended hepatic resections in a major hepatobiliary centre.

Methods: Details of patients undergoing standard and extended hepatic resections in a regional hepatobiliary unit between October 1988 and September 2000 were reviewed.

Results: There were 185 standard hepatectomies (85 men, 100 women) and 54 extended hepatectomies (29 men, 25 women) performed. The median age was 55 years (range 19–82 years) for the standard group, and 61 years (range 24–78 years) for the extended group ($P = 0.048$). 63 per cent of standard hepatic resections were performed for malignant disease (colorectal metastases 63 per cent, cholangiocarcinoma 15 per cent, others 22 per cent, compared with 85 per cent of extended hepatectomies (colorectal metastases 56 per cent, cholangiocarcinoma 23 per cent, others 20 per cent) ($P = 0.002$). The remaining standard hepatectomies (37 per cent) were performed for hepatic cysts (32 per cent), benign non cystic lesions (62 per cent) and trauma (6 per cent); whereas the remaining extended hepatectomies (15 per cent) were undertaken for hepatic cysts (25 per cent) and benign non-cystic lesions (75 per cent). Major perioperative morbidity occurred in 21 per cent of standard hepatectomy patients and in 33 per cent of patients undergoing extended resection. Minor complications occurred in 30 per cent and 25 per cent of patients repectively. There were eight postoperative deaths (< 1 month postoperation); four patients (2 per cent) following standard resections and four patients (7 per cent) following extended resections. Median postoperative stay was 11 days for the standard procedure and 15 days for the extended operation ($P < 0.0001$). Using the Kaplan–Meier point estimation, the overall median predicted survival was 66 months for all patients undergoing a standard resection (CI = 52–79) and was 47 months for all patients undergoing an extended resection (CI = 12–82) ($P = 0.02$ log rank test). The median predicted survival for patients with colorectal metastases following standard resection was 66 months (CI = 38–94) compared to 23 months (CI = 13–33) for extended resections ($P = 0.009$ log rank test).

Conclusion: There were differences in the indications for performing a standard or extended hepatectomy; the incidence of postoperative complications was similar in the two groups of patients although postoperative hospital stay was significantly longer following extended hepatic resection. Survival following extended resection was significantly less than for patients undergoing standard resection and may reflect more advanced pathology.

HPB 0010

Surgery for recurrent hepatic or other visceral metastases from colorectal cancer. Is it worthwhile?

J.B. Ward, A. Radtke, K. Cummins and A. Wu

Department of Surgery, University Hospital Aintree, Liverpool, UK

Aims: Hepatic resection for colorectal metastases has been demonstrated to be beneficial in many cases, but recurrence following such treatment generally has a bad prognosis. The aim of this study was to assess the results of repeat hepatic or other visceral resection for recurrent metastases.

Methods: Patients under follow-up after liver resection for colorectal metastases who developed recurrent metastases in the liver or other organs, were assessed for repeat resection. Those with local recurrence and peritoneal disease were excluded. Outcome in those undergoing repeat resection was examined.

Results: Eighteen patients being followed up after hepatic resection for colorectal metastases underwent surgery for recurrent hepatic or other visceral metastases. Thirteen patients underwent one further operation, five had two further resections. 10 patients had repeat liver resections (one twice), six lung resections, three splenectomies, one partial pancreatectomy and one cerebral metastasectomy. Two of these patients have also had recurrent local omental disease excised. In this group of patients there were no serious postoperative complications and no hospital deaths. At the time of analysis, six patients were known to have died, 29.5 months (median) post primary colonic resection (range 14–49), 23 (12–40) months after initial hepatic resection, and 12.5 (9–21) months after the final resection. Of those still alive 10 are clinically and radiologically clear of disease 57.5 months (median) after initial colorectal surgery (range 18–124 months), 43 (16–58) months after their first hepatic resection, and 22 (6–42) months after the last resection. Four of these patients have had a total of three separate resections of metastases. The other two surviving patients have recurrent local or bone metastases and are receiving chemo/radiotherapy 45 and 75 months after their initial disease, 10 abd 22 months after their last operation.

Conclusion: Although the results of surgery for recurrent colorectal disease in the liver and other viscera have variable outcome, a small number of cases may be considered for further resectional surgery with acceptable results and increased survival benefit.

HPB 0011

Right hepatic trisectionectomy: experience in 85 cases for advanced tumours

K. Menon, K.V. Ravindra, N. Ahmad, M. Attia, K.R. Prasad, G.J. Toogood and J.P.A. Lodge

Hepatobiliary Unit, St James's University Hospital, Leeds, UK

Aim: Right hepatic trisectionectomy is one of the most major hepatectomies and involves resection of hepatic segments 4,5,6,7 and 8 ± 1.

Methods: During 1993–9 we carried out 85 right hepatic trisectionectomies for metastasis ($n = 55$), cholangiocarcinoma ($n = 10$), hepatocellular carcinoma ($n = 5$), benign lesions ($n = 6$), other liver tumours ($n = 9$) in patients aged 21–76 years and with at least one year's follow-up. Our technique has been based on: (1) extrahepatic division of the right portal pedicle and right hepatic vein; (2) ultrasonic parenchymal dissection with intrahepatic division of the segment 4 pedicles and middle hepatic vein; (3) selective use of hepatic ischaemia. Concomitant caudate (segment 1) lobectomy was performed in 20 patients. Additional nonanatomic hepatic resections of the residual segments (1–3) were necessary in 17 patients (20 per cent). Bile duct excision and hepaticojejunostomy was needed in 23 patients, and associated resections included diaphragm ($n = 11$), large bowel ($n = 5$) and IVC/right atrium ($n = 6$, 4 *ex vivo*). Pringle's manoeuvre was needed in 31 (36 per cent) and hepatic vascular exclusion in 10 patients (11 per cent). 45 (53 per cent) patients required blood transfusion (median 2 units).

Results: There were two deaths within 7 days (2.4 per cent). A further eight patients (9.4 per cent) died within 60 days, reflecting the late stage of tumour presentation in our series. There have been 16 late disease-related deaths (19 per cent) after 2–41 (mean 12) months. 59 patients (69 per cent) are alive at 12–92 (mean 39) months, two following further hepatic resection. Detailed analyses will be presented.

Conclusion: Right hepatic trisectionectomy, although technically straightforward, remains a formidable operation. This series includes a high rate of associated resection of additional hepatic and extrahepatic disease.

HPB 0012

Hepatic resection for colorectal metastases in elderly patients

S.T. Yeung, T.G. John, M. Rees, J.G. Wells and S. Bygrave

Department of Hepatobiliary Surgery, The North Hampshire Hospital NHS Trust, Basingstoke, Hampshire

Aims: Concerns regarding the outcome of liver resection in elderly patients with colorectal liver metastases (CLM) were addressed by subgroup analysis of a large single-centre experience.

Methods: Prospective data from 500 consecutive liver resections performed between November 1986 and November 1999 were analysed. Of 387 liver resections for CLM, two subgroups were defined: patients age < 65 years (Group A: $n = 250$) and those age ≥ 65 years (Group B; $n = 137$). Demographic data, ASA grade, operative blood loss, morbidity and

mortality rates and 1, 3 and 5-year cancer-specific survival for patients followed for at least 1 year were compared (Kaplan–Meier method)
Results: There were no significant differences between groups A and B with respect to median blood loss (380 mL *versus* 370 mL), major morbidity (3 per cent *versus* 5 per cent) or operative mortality (1 per cent *versus* 2 per cent) The overall cumulative 1, 3 and 5 years survival for groups A and B were 90 per cent, 60 per cent and 39 per cent and 92 per cent, 49 per cent and 20 per cent for the over 65 age group ($P = 0\ 056$, log rank test $= -1.59$)
Conclusion: Major hepatic resections for CLM may be achieved safely with extended survival in elderly patients treated in specialist surgical units However, overall survival is inferior when compared with younger patients

ASGBI: Vascular 13–24

Friday 27 April 2001 14:15–16:05

Vascular 013

A new MRI technique to detect high-risk carotid plaque in patients with cerebral ischaemia

R.E. Murphy,[1] A.R. Moody,[1] S.T. MacSweeney,[2] W. Tennant[2] and J. Lowe[3]

Departments of [1]Academic Radiology, [2]Vascular Surgery, and [3]Pathology, Queen's Medical Centre, University of Nottingham, UK

Aims: A novel MRI sequence has been developed that can detect thrombus *in vivo*, showing it as high signal. We aimed to see if the technique can demonstrate intraplaque haemorrhage in carotid atheroma and thereby help to characterize plaques at high risk of embolization.

Methods: Nineteen patients undergoing assessment for carotid endarterectomy for symptomatic 70–99 per cent stenosis were imaged with the technique pre-operatively. The excised arteries were then histologically classified as American Heart Association type VI complex plaque (containing haemorrhage) or type V fibroatheromatous plaques. These were correlated with the MRI scans.

Results: Fourteen of nineteen plaques were type VI and 5/19 were type V. 13/14 of the complex plaques were positive for high signal and one was negative. 4/5 type V plaques were negative and one was positive (two-tailed Fisher's exact test, $P = 0.006$). These give a sensitivity of 92.8 per cent and a specificity of 80 per cent for the technique to detect complex plaque.

Conclusion:: This thrombus imaging sequence can identify patients who have complex carotid atheroma and are hence at highest risk of recurrent ischaemic symptoms. It may be of value in directing surgical interventions and plaque stabilising medical therapies in borderline surgical cases.

Vascular 014

The clinical and cost effectiveness of treating claudication

I.C. Chetter, J.I. Spark, P.J. Kent, D.C. Berridge, D.J.A. Scott and R.C. Kester

Dept of Vascular Surgery, St James's University Hospital, Leeds

Aims: This prospective observational study aims to assess the clinical and cost effectiveness of different treatments for intermittent claudication.

Methods: We studied 4 groups of claudicants: 34 undergoing conservative medical therapy (CMT); 33 undergoing a supervised exercise programme (SEP); 117 undergoing percutaneous transluminal angioplasty (PTA); and 33 undergoing surgery. Clinical effectiveness was analysed by calculating the number of quality adjusted life years (QALYs) gained at 12 months and 5 years using EuroQoL time trade off index measured prior to and 6 months following intervention. Cost/QALY for each intervention were calculated using recommended discount rates.

Results:

	QALYs gained				Marginal cost per QALY gained (£)			
	CMT	SEP	PTA	Surgery	CMT	SEP	PTA	Surgery
1 year	0.07	0.07	0.18	0.21	23 843	27 357	20 111	30 186
5 years	0.41	0.41	0.61	0.74	5961	6839	6582	9605

Conclusion: PTA and surgery are clinically effective in the treatment of claudication. The use of PTA as a primary treatment for claudication is further supported by the economic analysis.

Vascular 015

Can duplex sonography replace angiography in patients with intermittent claudication?

D. Phillips, A. Handa, J. Walton, V. Martin, J. Collin and L. Hands

Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK

Aims: To examine the effect of using duplex sonography to replace diagnostic angiography in patients with intermittent claudication.

Methods: In a prospective study from 1 October 1997–31 September 1999, 480 patients with intermittent claudication underwent lower limb arterial duplex sonography as part of an ongoing claudication assessment programme. 121 of these patients subsequently underwent angiography and the results were independently compared. Each examination was divided into 11 arterial segments and the presence or absence of significant disease (stenosis of greater than 50 per cent or occlusion) recorded.

Results: In eight patients duplex sonography of the aorto iliac segments failed leaving 1039 segments for comparison. The results are shown in the table.

Table 1 Duplex *versus* angiographic findings in different arterial segments

	Aorto-iliac	Common femoral	Superficial femoral	Popliteal
n	283	190	190	190
Sensitivity	0.85	1	0.97	0.92
Specificity	0.92	0.96	1	0.97

Overall there was agreement between duplex and angiography in 95 per cent of arterial segments. The sensitivity of duplex sonography compared with angiography was 93 per cent and the specificity 96 per cent. The kappa statistic was 0.87 indicating very good agreement.

Conclusion:: Arterial duplex sonography correlates well with angiography. Angiography can be reserved for those patients requiring an interventional procedure or where duplex sonography fails to adequately demonstrate the iliac arteries.

Vascular 016

Treating claudication: the impact on quality of life

I.C. Chetter, J.I. Spark, P.J. Kent, D.C. Berridge, D.J.A. Scott and R.C. Kester

Dept of Vascular Surgery, St James's University Hospital, Leeds, UK

Aims: This prospective observational study aims to compare and contrast the effects on quality of life (QoL) of different treatments for intermittent claudication.

Methods: We studied four groups of claudicants: 34 undergoing conservative medical therapy (CMT); 33 undergoing a supervised exercise programme (SEP); 117 undergoing percutaneous transluminal angioplasty (PTA); and 33 undergoing surgery. QoL was assessed using the Short Form 36 (SF36), prior to and 6 months post-intervention. The SF36 measures: physical functioning (PF) and role (RP), social functioning (SF), emotional role(RE), mental health (MH), vitality (V), pain (P) and general health (GH). SF 36 results are presented as standard scores.

Results:

	CMT		SEP		PTA		Surgery	
	Pre	6 months	Pre	6 months	Pre	6 months	Pre	6 months
PF	−0.8	−1.1	−0.85	−0.75	−1.1	−0.7*	−1.3	−0.45*
RP	−0.65	−0.65	−0.7	−0.7	−1.0	−0.65*	−1.0	0.0*
BP	−0.8	−0.8	−0.8	−0.5*	−0.8	−0.5*	−1.2	−0.15*
Vit	−0.3	−0.5	−0.45	−0.55	−0.75	−0.45*	−0.85	−0.1*
SF	−0.95	−1.3	−0.8	−0.6	−1.5	−0.8*	−1.5	0.0*
MH	−0.45	−0.45	−0.2	−0.3	−0.5	−0.5	−0.25	0.0

$^*P < 0.05$, Wilcoxon matched pairs test.

Conclusion: Pre-interventional QoL in claudicants undergoing PTA and surgery is inferior to those undergoing CMT and SEP, thus surgeons are selecting the most invasive management for the most incapacitated claudicants. CMT and SEP have little impact on QoL. PTA and surgery both improve QoL, however, only with surgery does postoperative QoL approach that of a matched population.

Vascular 017

Subintimal angioplasties – five-years' clinical follow-up in a single unit including all the 'learning curve'

C.D. Rodd, A. Saini, K. Lotzof, A.J. Marcus and R.L. Bird

Barnet and Chase Farm NHS Trust, UK

Aims: To audit primary radiological and clinical success, and subsequent outcome of all subintimal angioplasties, performed for long segmental femoro-popliteal occlusions, in a single unit.

Methods: The X-rays and the case notes of all subintimal angioplasties were reviewed.

Results: From March 1995 to July 2000, 56 patients between the ages of 51 and 92 years, underwent 66 subintimal angioplasties

Primary outcome	No	Secondary outcome	No
Primary radiological success = 66 per cent			
Primary clinical success	19	Walking	15
		Ulcer healing	3
		Chemical sympathectomy	1
Primary clinical failure	1	Chem symp and maj amputation	1
Secondary clinical failure	5	Pt asymptomatic	2
		Bypass procedure	1
		Repeat PTA	2–1 Rad Succ
No follow-up records	9		
Primary radiological failure = 34 per cent			
Bypass procedure	8	Died	3
		Amputation	1
		Good outcome	2
		Lost to follow-up	1
Repeat PTA	5	Good outcome	3
(4 Rad Success)		Lost to follow-up	1
(1 Rad Failure)		Bypass procedure	1
Chem symp	1		
Conservative mx	2	1	
No follow-up records	6		

Conclusion: Subintimal angioplasty is possible in a DGH and our results continue to improve with the learning curve. Our experience of primary failure with poor outcome has enabled us to define criteria for appropriate case selection

Vascular 018

Comparison of vein and prosthetic grafts for femoro-crural bypass

B Lindsey, C J Vickery, N S Balaji, C Cosgrove and S Ashley

Vascular Surgery Unit, Derriford Hospital, Plymouth, UK

Aim: It is widely accepted that autologous vein graft is the optimal conduit for femorocrural reconstruction. The purpose of this study was to compare the performance of vein and prosthetic grafts in a consecutive, non-randomized series of femoro-crural reconstructions performed within a single vascular firm

Methods: A 5-year series of 103 femoro-crural reconstructions in 97 patients (56 female, 41 male), median age 75 years (range 44–94 years), with critical ischaemia, performed by one surgeon, was analysed. A prosthetic conduit (PTFE or Heparin-bonded Dacron) was used if autologous vein was deemed inadequate on duplex scanning (<3mm), or at the time of harvesting All distal prosthetic graft anastomoses were performed using a vein cuff Pre-operative run-off was scored on the basis of duplex imaging or angiography for each calf vessel minimum score 0, maximum score 6 for each limb Duplex scanning or the presence of a palpable distal pulse confirmed graft patency.

Results: Mean follow up was 3 years There were 52 limbs with vein grafts and 51 limbs with prosthetic grafts Median age was similar in the vein (78 years) and prosthetic groups (76 years) as were median pre-op run-off scores (3) 1-, 2-, 3- and 4-year vein and prosthetic cumulative primary patency rates were 61 per cent, 57 per cent, 57 per cent and 45 per cent and 68 per cent, 63 per cent 48 per cent and 48 per cent, respectively Kaplan–Meier survival analysis showed no significant difference in cumulative primary patency rates between the two groups ($P = 0.50$ log rank statistic for equality of duration of patency)

Conclusion: These data suggest that the difference between vein and prosthetic grafts for distal bypass may not be as great as expected

Vascular 019

Is there still a place for aortic surgery in patients with aorto-iliac occlusive disease?

M M Flett, H.C Smith, D S Byrne, A J McKay, R O Quin and P N Rogers

Vascular Unit, Gartnavel General Hospital, 153 Great Western Road, Glasgow G12 0YN, UK

Aims: In 1998 the Scottish Audit of Surgical Mortality (SASM) reported a high mortality rate (20 per cent) in a total of only 46 patients who underwent elective aortic surgery for occlusive disease, in Scotland in 1997 This report has significant implications for the practice of aortic surgery, particularly in patients with intermittent claudication and, in view of this, we carried out a review of the treatment of aorto-iliac occlusive disease in our hospital

Methods: Since 1990, all patients undergoing in-patient treatment in the department of surgery have been recorded in a prospectively gathered database This database was used to identify all patients who underwent treatment for aorto-iliac occlusive disease The information collected on each patient included age and clinical presentation, length of hospital stay, outcome on discharge, complications, and peri-operative death

Results: A total of 823 patients underwent treatment in the 10-year period, from 1990 to 1999 172 patients underwent aorto-bifemoral bypass, 517 patients had endovascular intervention, in the form of a percutaneous transluminal angioplasty or stent and 134 extra-anatomic bypasses were carried out Of the 172 patients who underwent aorto-bifemoral bypass, there were 6 perioperative deaths (3.5 per cent) The indications for surgery were intermittent claudication in 126 patients and critical limb ischaemia in 46 patients There was one death in the group with intermittent claudication (0.8 per cent). There was no significant change in the numbers of patients undergoing aortic surgery during this period there were 38 patients in the 2-year period 1990/91 and 36 patients in 1998/99 Over the same time period, there was a steady increase in the number of endovascular procedures 59 procedures were performed in 1990/91, compared with 143 in 1998/99 In our unit, the increase in percutaneous endovascular treatment has not coincided with a decrease in surgical intervention, but has resulted in an increase in the total number of patients being treated for aorto-iliac occlusive disease.

Conclusion:: The data from our unit alone suggests that coding by the Information and Statistics Division of the NHS has significantly under-estimated the number of aortic surgical procedures being carried out in Scotland and, the resulting mortality rate reported by the SASM is misleadingly high. In our experience aorto-bifemoral bypass is a safe procedure with low perioperative mortality and, we believe, remains an appropriate treatment for carefully selected patients with symptomatic aorto-iliac occlusive disease, unsuitable for endovascular intervention

Vascular 020

Patency following successful thrombolysis of occluded vascular grafts

R B Galland, T.R Magee, J J Earnshaw, B Whitman, G Hamilton, C Judge, J H N Wolfe and M Kerle

Royal Berkshire Hospital, London Road, Reading, UK

Aims: To determine patency after successful lysis of occluded bypass grafts

Methods: Data were collected from four centres with a wide experience of thrombolysis. Outcome following successful lysis was determined from prospectively collected data or case notes.

Results: Data from 75 patients, 53 men, were analysed Median age at time of lysis was 68 years (range 33–88). Median age of graft was 12 months (range 1–120). Patency at 1 year and 2 years was 32 per cent and 22 per cent, respectively In 48 cases lysis was deemed complete (1 year's patency 32 per cent *versus* 30 per cent for incomplete) 17 grafts were above the inguinal ligament (patency at 1 year 58 per cent *versus* 27 per cent for below inguinal ligament) In 27 cases additional procedures were undertaken after successful lysis (percutaneous angioplasty 20, vein patch seven). Patency at 1 year was 33 per cent whether or not an additional procedure was carried out. At 6 months, patency for men (60 per cent) was twice that achieved for women.

Conclusion: It is difficult to justify thrombolysis of occluded grafts when patency, based on intention to treat, is approximately 20 per cent at 1 year

Vascular 021

Outcome after intra-arterial thrombolysis: value of POSSUM and a non-surgical technique

B. Neary, B Whitman, C. Foy, B.P Heather and J J Earnshaw

Gloucestershire Royal Hospital, UK

Aims: The aim was to see if the POSSUM scoring method would predict mortality and complications in intrarterial thrombolysis, a non-surgical procedure A previous study from the VSSGBI suggested that operative data did not affect the predictive power of POSSUM scoring

Methods: Since 1990, 141 consecutive patients have undergone 147 events of intra-arterial thrombolysis for acute leg ischaemia The case notes of these patients were reviewed retrospectively and POSSUM scored Outcome and complications were recorded

Results: The patients had a median age of 72 (range 44–91) years, the majority had ischaemic rest pain (Fontaine Grades IIa 1 (1 per cent), IIb 30 (20 per cent), III 107 (73 per cent), IV 9 (6 per cent)). Limb salvage occurred after 94 (67 per cent) procedures, amputation was required in 21 (14 per cent) and death occurred in 32 (22 per cent).

	Mortality risk band					
	0–4%	4–10%	10–25%	25–60%	>60%	Total
No of lysis events	58	45	26	10	8	147
No of deaths	1 (1.7%)	6 (13.3%)	12 (46.2%)	6 (60%)	7 (89%)	32 (22%)
No of major complications	3 (5.2%)	1 (2.2%)	2 (7.7%)	0	0	6

There was a significant relationship between POSSUM physiology score and mortality ($P < 0.001$ linear by linear association).
Conclusion:: POSSUM scoring predicted mortality in peripheral thrombolysis and could be used to improve informed consent.

Vascular 023

Adequate vascular training can be undertaken without compromising patient care

A. Handa, M. Pai, D. Phillips, L.J. Hands and J. Collin
Nuffield Department Surgery, John Radcliffe Hospital, Oxford, UK

Aims: To review the results of index operations in vascular surgery and to evaluate the impact of a specialist vascular training programme on patient outcome.
Methods: We undertook a 5-year (Jan 1995 – Dec 1999) review of the weekly collected mortality and morbidity data. The total number, 30 day mortality and stroke rate of all index operations, i.e. AAA repairs (ruptured and elective), CEA and infra-inguinal bypasses (above and below knee, elective and emergency) was recorded. The number of operations performed by trainees under supervision was recorded.
Results: The results are as shown in the table.

	Operation			
	AAA - ruptured	AAA - elective	CEA	Infra-inguinal bypass
Total no.	214	241	240	296
Trainee (%)	186 (86.7)	189 (78.4)	140 (58.4)	223 (75.5)
Consultant supervision (%)	107 (57.7)	159 (84.3)	140 (100)	201 (90.3)
Death (%)	112 (52.3)	8 (3.3)	4 (1.7)	43 (21.6)
Stroke rate (%)	N/A	N/A	14 (5.8)	N/A

Overall vascular trainees performed 75.5 per cent of the index operations of which 74.9 per cent were supervised.
Conclusion: Trainees under supervision performed three out of four index operations. The mortality and morbidity of index operations in our unit compared well with accepted best mortality and morbidity figures. Our unit appears to provide good training opportunities for vascular trainees whilst maintaining satisfactory standards of patient care.

Vascular 024

Methicillin-resistant *Staphylococcus aureus* (MRSA) in patients undergoing major amputation

S.A.J. Grimble, P. Burden, T.R. Magee and R.B. Galland
Royal Berkshire Hospital, London Road, Reading, UK

Aims: To examine the impact of MRSA infection on patients undergoing major amputation.
Methods: Patients having had major amputation and positive MRSA culture January 1995–December 1999 were included. Outcome was compared with a randomly chosen group of patients having major amputation but no positive MRSA cultures during the same time period.
Results: From 1995 to 1997 there was a steady increase in the number of patients undergoing amputation who had MRSA isolated. There was a fourfold increase 1997–98. Overall 21 per cent of patients undergoing amputation were MRSA positive. 28 patients (30 amputations) with MRSA positive cultures were compared with 44 patients (54 amputations) who did not have positive cultures for MRSA (controls). MRSA was isolated from the wound in 17 of 30 amputations. The patients were well matched for demographic and cardiovascular risk factors. More patients in the control group had a below knee amputation (38 of 54 compared with 12 of 30, $P < 0.02$). Mortality in MRSA positive patients was higher than controls (12 of 28, *versus* 4 of 44, $P < 0.01$). Primary healing was achieved in only four of 17 amputations where MRSA was isolated from the wound. This compared with 31 of 54 controls ($P < 0.05$). Delayed healing due to chronic infection was also more likely in MRSA positive patients ($P < 0.01$).
Conclusions: In view of the high morbidity and mortality in patients with positive MRSA isolates, specific antibiotic prophylaxis against MRSA should be considered in patients undergoing major amputation.

Poster Abstracts

Breast

Poster 001

MRI – the imaging modality of choice for invasive lobular breast cancers

K. Mumot, B. Dall, R Achuthan and K. Horgan
Leeds General Infirmary, Leeds, UK

Aims: Invasive lobular breast cancers present diagnostic challenges in clinical practice because of their imprecise palpable characteristics, diffuse nature and relative radiolucency leading to minimal mammographic abnormality The aim of this study was to determine whether MRI confers any advantages over conventional imaging in the diagnosis and determination of extent of invasive lobular breast cancers.
Methods: Dynamic contrast enhanced MRI scanning was performed on 50 patients with primary breast cancer prior to initial treatment There were 17 patients subsequently shown to have invasive lobular cancer and their MRI, mammography, ultrasound and histological characteristics were examined
Results: In 11 of the 17 (64.70 per cent) patients, MRI gave significant additional information about the extent of the tumour, which had an impact on surgical treatment. MRI accurately identified tumour in three patients who presented clinically with distortion of the breast without a palpable abnormality and with entirely normal imaging on both mammography as well as ultrasound. In three patients with known tumour MRI showed additional foci of tumour not apparent on conventional imaging and in four patients conventional imaging grossly underestimated the size of the tumour as compared to the extent on MRI.

Imaging modality	Sensitivity
Mammography	51 85%
Ultrasound	66 66%
MRI	96 3%

Conclusions: MRI has a higher sensitivity as compared to conventional imaging and by accurately assessing the size of primary tumours and extent of multicentric disease it also provides valuable information for preoperative planning and single-stage resection in invasive lobular breast cancers MRI of the breast is not widely available but shows specific advantages in the pre-operative characterization of invasive lobular breast cancers, which are increasingly being diagnosed pre-operatively with the use of outpatient core biopsies

Poster 002

Selective management of the axilla in operable breast cancer based on intraoperative contact cytology of sampled nodes is safe

M Burke, K I. Burke, S Boyle, A Price, K. Shah and C. Zammit
Northwick Park and St Marks' NHS Trust, UK

Aims: The aim of the study was to assess the long-term safety of a policy of performing axillary clearance (AC) only on patients with operable breast cancer with positive intraoperative contact cytology (DABS) on sampled lymph nodes or more than one cytology-negative, histology-positive node
Methods: Three hundred and four patients treated between 1992 and 1996 (216 DABS 86 DABS + AC) were followed up for 48–96 months. Patients with Nottingham Prognostic Index of 3 or more were given adjuvant medical therapy.
Results: In the DABS group there were 7/216 axillary and 0/216 supraclavicular recurrences compared to 3/86 axillary and 3/86 supraclavicular recurrences in the DABS + AC group Survival probability for the DABS (versus DABS + AC) group was 36 months, 92 per cent (85 per cent) 72 months, 87 per cent (73 per cent): 96 months, 84 per cent (71 per cent) [Pr > χ^2 = 0 0117]. Sampled nodes included 131/168 positive nodes and all positive nodes in 18/88 cases (including two nodes with negative cytology but positive histology). Six cases had discordant intraoperative cytology and histology. One developed axillary recurrence simultaneously with liver and brain recurrence.
Conclusions: Selective management of the axilla based on intraoperative contact cytology of sampled nodes allows good long-term control of regional lymph node metastasis and is associated with acceptable long-term survival

Poster 003

Patient demographics and treatment choices for early breast cancer

E V Williams, M. Hodin, P J. Drew, H Fielder[1] and H M Sweetland
The Cardiff Breast Unit & Dept Epidemiology & Public Health, UWCM[1], UK

Aims: To examine the relationship between selected patient demographics and treatment choice for early breast cancer, and to assess patient satisfaction with their choice of cancer therapy
Methods: The target population was a random selection of patients with early breast Ca $\leq$ T 2, N 1) who were offered a choice of surgery. These patients were identified at follow-up clinic and were interviewed by means of a designed questionnaire.
Results: Two hundred and two patients were interviewed with a mean age at time of treatment of 57 (32–90) years. 97 per cent were British and 3 per cent were from overseas 71 patients (35 per cent) choose mastectomy (Mast), 10 (5 per cent) mastectomy and reconstruction (M + R) and 121 (60 per cent) breast conserving surgery (BC) Prior to attending the breast clinic 36 per cent thought that mastectomy was the only treatment for breast Ca, and 22 per cent felt that this was a more effective treatment. 82 per cent were surprised at being asked to take part in choosing their treatment

	Mast	BC	P
Mean age (years)	61 (38–90)	55 (32–79)	<0 0001
Married/partner	66%	84%	0 009
Education (<16 years)	58%	41%	0 065
FH	10%	20%	0 02
Tumour size (mm)	17 (6–50)	15 (4–40)	0 014

Questions	%	Mast	BC
Sufficient information?	Yes	92	95
More time?	Yes	8	14
More painful?	Yes	17	29
More disfiguring?	Yes	58	40
Different Rx?	Yes	6	12

Conclusions: There was no association between quintile of deprivation, age of leaving education, surgeon or breast care nurse and treatment choice Increased patient age, increased tumour size, women without partners and those with no FH were associated with a greater likelihood of choosing mastectomy. Women thought they had enough information to make an appropriate treatment choice and they were satisfied with the information provided. They did not feel rushed to decide on therapy, nor was there a substantial likelihood to regret their choice of surgical treatment.

Poster 004

Validation of a digital image analysis system for objective assessment of ER status

R. Walsh, R. Mofidi,[1] P F. Ridgway, T. Crotty,[2] P McCarthy,[2]
S Sheehan, D Mehigan,[1] E.W McDermott, T.V Keaveny, M J Duffy,
A.D.K. Hill and N O'Higgins
Department of [2]Vascular Surgery, [1]Pathology, and the Surgical Professorial Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

Aims: The authors have previously described quantitative, computer-assisted analysis of oestrogen receptor status in immunohistochemically stained sections in patients with primary breast cancer The aim of this study is to validate the aforementioned system against the commonly used methods of assessing oestrogen receptor status
Methods: Paraffin embedded sections from 156 patients with primary breast carcinoma were stained with anti-α-oestrogen receptor monoclonal antibody (1D5) through standard immunohistochemical protocol Images from 10 high-powered fields were captured from each section using a digital camera mounted on a microscope at ×400 magnification and analyzed using *Adobe Photoshop* image analysis software. A nuclear mask was obtained through the digital selection of nuclear area Staining intensity in the nuclear mask was then analysed using red absorption characteristics Manual assessment of estrogen receptor status was performed through counting the percentages of cells that are positive from 200 randomly sampled nuclei from 10 HPF Cut-off value for positivity was taken as 10 per cent. Cytosolic oestrogen receptor concentration was measured through enzyme immunoassay (ELISA – Abbott ER-EIA Monoclonal System) Cut off value for ER positivity was taken as 200 fmol g^{-1} (wet tissue) Correlations between the

median optical density of the nuclear mask, subjectively measured percentage positivity and cytosolic ER concentration were expressed as a Pearson correlation coefficient and confirmed using linear regression analysis.

Results: One hundred and fifty-six sections were studied of which 41 were ER negative. Median percentage positivity in the remainder was 90 per cent (17–100) by manual assessment. The median red scale value was 108 (58–156). A close correlation was observed between median optical density of the nuclear mask and percentage positivity assessed manually ($r = 0.844$, $P < 0.001$). There was a significant correlation between the optical density of the nuclear mask and cytosolic oestrogen receptor concentration ($r = 0.748$, $P < 0.01$).

Conclusion: Oestrogen receptor positivity can be accurately assessed through digital image analysis. This process offers objective data regarding amount of oestrogen receptors within the nuclei as well as the percentage of nuclei that express oestrogen receptors.

Poster 005

A prospective randomized trial of multimodel therapy *versus* initial hormone therapy for locally advanced primary breast cancer (LAPC)

K.L. Cheung, S.M. Tan, P.C. Willsher, R.W. Blamey, S.Y. Chan and J.F.R. Robertson

*Professorial Unit of Surgery and *Department of Clinical Oncology, City Hospital, Nottingham, UK*

Aims: To compare two treatment approaches for LAPC.

Methods: A prospective randomized trial of multimodal therapy (neo-adjuvant chemotherapy, Patey mastectomy, postoperative radiotherapy and adjuvant hormone therapy) ($n = 56$) *versus* initial hormone therapy ($n = 52$) for LAPC was carried out with patients accrued between 1989 and 1994. The results at a median follow-up of 52 months (maximum 10 years) are reported.

Results: Compared to multimodal therapy, initial hormone therapy was associated with reduced number of therapies for disease control (mean = 3.6 *versus* 4.9), mastectomy rate (31 per cent) and treatment-induced morbidity. Multimodal therapy conferred better initial locoregional control and therefore longer disease-free interval. Nevertheless, there was no statistically significant difference in the rates of survival, metastasis and uncontrolled locoregional disease, as well as in the time to metastasis between the two therapy groups. Regardless of therapy groups, oestrogen receptor (ER) positivity conferred lower metastasis rate, better survival and locoregional control.

Conclusions: Initial hormone therapy is a reasonable option for managing LAPC, especially for ER-positive tumours.

Endocrine

Poster 006

Survey of the management of thyroid cancer in the North West

P. Dey, D. Arnold, E. Allen, P. Hindmarsh and N. Bundred

Centre for Cancer Epidemiology, University of Manchester, Christie Hospital NHS Trust

Aims: International variations in the management of this thyroid cancer exist. We have carried out a population-based survey of the management of thyroid cancer in Greater Manchester and Lancashire to assess compliance with current national management guidelines.

Methods: This was a population-based cross-sectional survey. Residents of Greater Manchester and Lancashire newly diagnosed with cancer of the thyroid during 1995 and 1996 were identified (n = 140) from data held by the North-west Regional Cancer Registry (NWRCR). Information on the following was abstracted from case records and the NWRCR: demographic characteristics; tumour type; referral patterns; uptake of investigations and treatment modalities.

Results: Case records were unavailable for 12 patients who were excluded from further analysis. 50 (39 per cent) of the 128 patients available for analysis were under 45 years of age. 89 (46 per cent) patients had papillary carcinoma, 26 (21 per cent) follicular carcinoma and 11 (9 per cent) mixed tumours. 93 (73 per cent) were initially referred to a general surgeons and eight (6 per cent) to an ENT surgeon. 40 (61 per cent) consultants diagnosed one or fewer thyroid cancers per year. Only 54 (42 per cent) patients had fine needle aspiration cytology of which 11 were reported to be benign or unsatisfactory. 82 (72 per cent) had preoperative vocal cord checks. 30 (55 per cent) consultants operated on one or fewer patients with cancer of the thyroid per year. 63 (49 per cent) patients had total thyroidectomy and 71 (56.2 per cent) iodine ablation. 27 per cent of patients were referred to three different consultants before they were treated.

Conclusions: Management of thyroid cancer remains variable and the majority of patients do not receive a preoperative diagnosis or appropriate surgical management. Compliance with published national guidelines remains patchy.

Upper Gastrointestinal

Poster 007

The use of CT scanning to evaluate the response of oesophageal tumours to chemoradiotherapy

D.M. Beardsmore, M. Sheridan,[1] A. Crellin,[2] H. Sue-Ling, P.J. Guillou and G.W.B. Clark

Department of Surgery, Radiology and Oncology, St James's University Hospital, Leeds, UK

Aims: Overall, patients who receive neoadjuvant chemoradiotherapy for oesophageal cancer are afforded a survival advantage but response between individuals is varied. We evaluated the response of oesophageal tumours to chemoradiotherapy by examining the CT scans before and after treatment.

Methods: Twenty-three patients with T3 tumours were recruited into a phase II clinical trial of chemoradiotherapy followed planned surgical resection. Patients were classified into four groups: (1) complete responders (no residual tumour in the resection), (2) responders (< T3 following resection), (3) non-responders (T3 following resection) and (4) tumour progression (CT evidence of metastases). The maximal transverse and antero-posterior (AP) primary tumour diameters in corresponding anatomical planes were measured from the CT scans before and after treatment. The percentage reduction (−) or increase (+) in maximal tumour diameter was calculated.

Results:

	Transverse change (per cent)	AP change (per cent)
Progression	−9.9	−5.6
(4)	(−38.5–28.9)	(−21.1–34.7)
Non-responders	13.7	0.4
(5)	(−30–45.8)	(−27.2–28.6)
Responders	−22.3	−26
(8)	(−57.5–104)	(−51.4–40.9)$^{\varphi}$
Complete response	−44.1	−40.9
(6)	(−63 to −24.4)$^{*\#}$	(−80.3 to −13)$^{\psi\Sigma}$

(Mann–Whitney U-test: complete responders *versus* non-responders $^{*\psi}P = 0.01$; complete responders *versus* progression $^{\#}P = 0.03$ and $^{\Sigma}P = 0.05$; responders *versus* non-responders $^{\varphi}P = 0.04$)

There was a significant difference in change in both diameters for complete responders compared to non-responders and to the progression group and also in the AP diameter between responders and non-responders. By examining the maximum change in diameters we found that a reduction of > 30 per cent of the tumour predicted complete responders and responders from non-responders with a sensitivity of 85.7 per cent of and a specificity of 100 per cent.

Conclusions: CT scanning following chemoradiotherapy is essential not only in detecting metastases but also provides information regarding the down-staging of the primary tumour. However, CT cannot distinguish a partial from a complete response and therefore surgery is still justified.

Poster 008

Dysphagia after laparoscopic antireflux surgery: what is the true role of fundoplication in its production?

A.C. de Beaux, D.I. Watson, C. O'Boyle and G.G. Jamieson

University Department of Surgery, Royal Adelaide Hospital, North Terrace, South Australia

Aims: Dysphagia following antireflux surgery is often seen as an unavoidable sequelae of surgery. This study undertook a detailed evaluation of dysphagia before and after laparoscopic fundoplication.

Methods: Three hundred and twelve patients undergoing laparoscopic fundoplication underwent prospective assessment of dysphagia using a composite dysphagia score (score 0 – no dysphagia; score 45 – complete dysphagia) at structured interview before and 6 months after surgery.

Results: The median dysphagia score was 0 (range 0–40) pre-operatively and 0 (range 0–45) 6 months post-operatively. Overall, 98 (32 per cent) patients' dysphagia score improved, 132 (42 per cent) patients' dysphagia score

remained unchanged and 82 (26 per cent) patients' dysphagia score deteriorated 6 months after surgery. 188 (60 per cent) patients had no dysphagia (a score of 0) before surgery. Six months after surgery, 59 (31 per cent) of these patients noted varying degrees of dysphagia. 124 (40 per cent) patients had a dysphagia score >0 before surgery. 98 (79 per cent) patients dysphagia score improved, three (2.4 per cent) patients dysphagia score remained unchanged and 23 (19 per cent) patients dysphagia score deteriorated 6 months after surgery. In 44 patients with dysphagia before surgery, their score fell to 0 (i.e. no dysphagia) at 6 months after surgery.
Conclusion: Dysphagia is a common symptom prior to fundoplication. After fundoplication, new or worsening dysphagia is more likely to occur in patients with no dysphagia pre-operatively. Furthermore, those patients with dysphagia prior to surgery are more likely to have an improvement in their dysphagia rather than a deterioration following fundoplication.

Hepatobiliary/Pancreatic

Poster 009

Pancreatic resections – appropriate procedures for District General Hospitals?

G Heriot, K Rose, R.C Bowyer,[1] I Paterson[2] and N Karanjia
Royal Surrey County Hospital, Guildford, [1]St Richards Hospital, Chichester, [2]Frimley Park Hospital, Frimley, UK

Aims: Studies have suggested that all pancreatic resections should be performed in specialist pancreatic units as results from district units are inferior. The aim of this study was to assess the outcome of this surgery by three consultant surgeons with a hepatopancreaticobiliary interest working in three adjacent district general hospitals.
Methods: The notes of all pancreatic resections performed by the three consultant surgeons since their appointments were reviewed. The surgical procedure, complications, histology and outcome were assessed.
Results: Over a total duration of 17 years since the appointments of the consultants, 86 patients (mean age 59 years, SD 14 years) have undergone pancreatic resections. Thirty-eight patients underwent Whipple's resections, 35 pylorus-preserving pancreaticoduodenectomies, 11 distal pancreatectomies, one total pancreatectomy, and one local excision of the ampulla. Seven patients underwent vascular reconstruction (five portal vein, two superior mesenteric vein, one superior mesenteric artery) during their resection. Postoperative complications necessitated reoperation in seven patients (8 per cent) and two patients developed pancreatic fistulas that closed spontaneously. There were five (5.8 per cent) deaths in hospital. There were 32 ductal adenocarcinomas, 14 ampullary adenocarcinomas, and 8 cholangiocarcinomas. A survey of specialized units in the UK have reported a reoperation rate of 6 per cent and a mortality of 6 per cent.
Conclusions: The results of pancreatic resections for tumours by consultants with a particular interest in pancreatic surgery in district general hospitals compare favourably with results from specialized centres. Centralisation of pancreatic resections may not be necessary provided surgeons performing resections have an interest in hepatopancreaticobiliary surgery and adequate oncological services.

Poster 010

SPINK 1/PSTI mutations are associated with acute and chronic pancreatitis

A D O'Reilly, H Witt, K Sargen, A Kage, M T Cartmell, M Becker and A N. Kingsnorth
Department of Surgery, Derriford Hospital, Plymouth, UK & Department of Paediatrics, Charité, Humboldt University, Berlin, Germany

Aims: Recent genetic research has focused attention upon the role of the protease/protease inhibitor system in the pathogenesis of pancreatitis. This study investigates the prevalence of the recently described N34S mutation, within the trypsin inhibitor gene, SPINK 1/PSTI, in acute and chronic pancreatitis.
Methods: One hundred and thirty-five patients with acute pancreatitis, 66 with chronic pancreatitis, 214 ethnically matched controls (including 71 alcoholic controls) were genotyped for the presence of the N34S mutation, by polymerase chain reaction and melting curve analysis.
Results: The presence of the SPINK 1/PSTI mutation was detected in 5/135 patients with acute pancreatitis ($P = 0.008$), 3/77 patients with acute gallstone pancreatitis and 2/34 patients with acute idiopathic pancreatitis ($P = 0.017$ and $P = 0.017$, respectively), with respect to controls. It was also detected in 4/66 patients with chronic pancreatitis ($P = 0.002$), 3/47 with alcoholic CP ($P = 0.005$) and 1/16 with idiopathic chronic pancreatitis but was not detected among any of the 214 ethnically matched controls.
Conclusions: This study describes the association of the N34S mutation of the SPINK 1/PSTI gene with acute and chronic pancreatitis. These findings support the importance of premature protease activation in the pathogenesis of pancreatitis and suggest that a genetic alteration to the trypsin inhibitor, SPINK 1/PSTI, may predispose certain individuals to develop this condition.

Poster 011

Operative treatment of juvenile chronic pancreatitis

R J Obholzer, R.S Hart and R C N Williamson
Hammersmith Hospital, DuCane Road, London W12 0HS, UK

Aims: To assess long-term outcome in young patients undergoing operation for painful chronic pancreatitis by the age of 25 years.
Methods: A personal series of 19 patients with juvenile (idiopathic) pancreatitis was reviewed in terms of presentation, treatment and outcome. This group represents less than 10 per cent of those operated for chronic pancreatitis in this unit.
Results: Nineteen patients (11 male, eight female) underwent operation for juvenile chronic pancreatitis between 1981 and 1999. Mean age at onset of symptoms was 15 years (range 4–23 years), while mean age at operation was 20 years (8–25 years). The indication for operation was disabling pain in all but one patient who had jaundice due to severe disease in the head of the pancreas. The aetiological cause was unknown in 17 patients, but was clearly hereditary in two with a strong family history who carried the n291 cationic trypsinogen gene. Eleven patients underwent pancreatic resection and 8 a drainage operation. Resections were distal ($n = 5$), proximal (pylorus-preserving pancreatoduodenectomy, $n = 3$) and total (3). Seven patients received longitudinal pancreaticojejunostomy and one, transduodenal sphincteroplasty. At a mean follow-up of 9.3 years (range 0.5–18 yr), there have been no deaths and 12 patients remain pain-free. Four of seven patients with persisting pain on follow-up, require regular opiate therapy, three having relapsed after initial relief of pain.
Conclusions: The distribution and severity of chronic pancreatitis during childhood resemble those of the adult variant. Nearly two-thirds of affected patients can enjoy long-term pain relief as a consequence of a major surgical operation.

Poster 012

Emergency laparoscopic cholecystectomy in acute cholecystitis

M Heitmann and P Super
Dept of General Surgery, Birmingham Heartlands Hospital, Birmingham, UK

Aims: To demonstrate that emergency laparoscopic cholecystectomy is safe in acute cholecystitis.
Methods: Data were prospectively collected of all laparoscopic cholecystectomies undertaken under one consultant during a 16-month period. Emergency patients with acute cholecystitis had a laparoscopic cholecystectomy performed within 5 days of onset of symptoms.
Results: A total number of 149 laparoscopic cholecystectomies were performed during the 16-month period. No operations were converted to open surgery in either group. 131 (87.92 per cent) elective and 18 (12.08 per cent) acute cholecystectomies were performed. Elective patients stayed in hospital for a mean 1.4 days (range 1–18 days). Acute patients stayed in hospital for a mean 2.6 days (range 1–5) postoperatively. There were no complications in the emergency admission group. Complications in the elective group included one bile leak from cystic duct stump treated conservatively and one bile leak from an accessory cystic duct requiring open exploration and drainage on day 2, followed by ERCP on day 5. There was no mortality.
Conclusions: Emergency laparoscopic cholecystectomy is a safe procedure in acute cholecystitis especially if performed early in the disease process. This is not associated with a higher complication rate.

Poster 013

Laparoscopic cholecystectomy without clipping the cystic artery is safe

M Douek, M Kyaw and N R Fieldman
Newham General Hospital, Plaistow, London E13 8SL, UK

Aims: The safety of leaving the cystic artery unclipped and simply using diathermy on its terminal branches was assessed in a prospective series

Methods: Over a period of 12 months, laparoscopic cholecystectomies, performed by one consultant surgeon operating on all patients in the French position, were studied. Hook diathermy was used throughout. The cystic artery and cystic duct were identified in Calot's triangle. All gallbladder branches of the cystic artery were followed to the gallbladder wall, and divided using the diathermy hook. The main trunk of the cystic artery was only clipped if it was considered unsafe not to do so. The cystic duct was divided between two proximal absorbable clips (Absolok, Chroma, UK) and one distal metal Ligaclip (Ethicon, Somerville, USA). Inpatient hospital stay, operative time, intra-operative bleeding, morbidity and mortality were assessed prospectively.
Results: A total of 75 patients, median age 46 years (range 23–84), were recruited. Mean inpatient hospital stay was 1.5 ± 0.9 days (mean ± SD) and of these seven (9 per cent) were performed as day cases. Of 75 patients, in 54 (72 per cent) the cystic artery was divided using only diathermy division of its branches. In 21 patients (28 per cent) the artery was secured proximally using an Absolok absorbable clip. Of these, the cystic artery was clipped because the main trunk was large ($n = 14$), there were two or more arteries ($n = 2$), the patient was hypertensive intra-operatively ($n = 2$), the cystic artery was thick and short ($n = 1$), the cystic artery was sclerosed ($n = 1$) or the dissection of Calot's triangle was difficult ($n = 1$). One patient was converted to open cholecystectomy because of extensive fibrosis of the gallbladder and none required re-operation due to haemorrhage. The average estimated blood loss was 7 ± 11 mL (mean ± SD). In three patients, discharge was delayed due to post-operative pain. In those patients operated laparoscopically (74/75) there were no other complications at a minimum of 6 weeks follow-up.
Conclusions: In the majority of cases, the cystic artery can be safely divided using diathermy division of its branches alone.

Poster 014

Experience with left trisectionectomy in 30 patients with extensive hepatic malignancy

K.V. Ravindra, N. Ahmad, K. Menon, M. Attia, K.R. Prasad,
G.J. Toogood and J.P.A. Lodge
Hepatobiliary Unit, St James's University Hospital, Leeds, UK

Aims: Left hepatic trisectionectomy involves resection of hepatic segments 2, 3, 4, 5 and 8 ± 1. It is one of the most difficult of the major hepatectomies. The absence of landmarks for the right fissure combined with anatomical variations of the right portal structure makes it technically hazardous. However, it remains a useful technique for resecting centrally located tumours and for hilar cholangiocarcinomas with predominant left duct involvement.
Methods: During 1993–2000 we carried out 30 left hepatic trisectionectomies for colorectal metastases ($n = 20$), cholangiocarcinoma ($n = 6$), hepatocellular carcinoma ($n = 3$), and neuroendocrine tumour ($n = 1$) in patients aged 30–77 years. Our technique has been based on: (1) division of the left portal pedicle; (2) division of the right anterior portal pedicle; (3) early division of the left and middle hepatic veins; (4) selective use of hepatic ischaemia; (5) ultrasonic parenchymal dissection.
Results: Concomitant caudate (segment 1) lobectomy was performed in 15 patients. Bile-duct excision and hepaticojejunostomy was required in nine patients. Whilst eight patients did not require vascular clamping, Pringle's manoeuvre (mean 63 min) was needed in 11 and hepatic vascular exclusion (mean 47 min) in five patients. 13 (43 per cent) patients required blood transfusion (mean 1.5 units). The transfusion requirement did not differ between the groups with and without vascular clamping. Significant morbidity occurred in seven patients, including bile leak in three patients. Three patients died within 30 days (10 per cent) early in the series. All complications occurred in patients who had required vascular clamping. Actuarial survival at 5 years is currently 33 per cent.
Conclusions: Left hepatic trisectionectomy remains a challenging procedure but it is a useful technique and results improve with experience.

Poster 015

The multimodal treatment of colorectal liver metastases

M.S. Javed, E. Harrison, A. Gillams, A. Amin, J. Ledermann, W. Lees
and I. Taylor
Royal Free and University College Medical School, University College London, UK

Background and aims: Fifty percent of colorectal cancer (CRC) patients develop liver metastases. Many therapeutic options including surgical resection, radio frequency or chemical ablation and systemic chemotherapy are available. The aim of this study was to assess whether a multidisciplinary and multimodal approach is effective in the management of patients with CRC liver metastases.
Methods: A prospective audit of 92 consecutive patients with CRC liver metastases discussed in a multidisciplinary meeting was carried out. Survival data was obtained.
Results: Ninety-two patients were followed up. Median age was 62 (38–82) years with 55 (60 per cent) males. Median follow up was 11 months. Twenty-one patients (23 per cent) underwent resection, of which seven patients also had radio frequency ablation and chemotherapy, 11 had systemic chemotherapy and one patient had RF ablation alone in addition to resection. Additionally 13 patients had RF ablation and chemotherapy, one RF ablation alone, 49 chemotherapy alone and eight patients had no specific treatment. There was no operative mortality in the resection group and the median survival of this group was 46 months. The median survival of the non-operative group was 14 months and median overall survival for the entire group was 21 months.
Conclusions: Forty per cent of patients with CRC liver metastases discussed in a multidisciplinary context received more than one modality of treatment. Resection is most effective but is combined with other treatment modalities such as RF ablation and chemotherapy with advantage. Patients with CRC liver metastases should have the benefit of multidisciplinary and multimodal management.

Gastrointestinal

Poster 016

Impact of a two-week waiting time standard on the gastroenterology service of a District General Hospital

S. Moreea, J. Green, J. MacFie and C.J. Mitchell
Combined Gastroenterology Services, Scarborough Hospital, UK

Aims: The 2-week waiting time standard for suspected gastrointestinal cancers came into effect in July 2000. There are concerns that this may overload already stretched resources leading to a longer wait for routine referrals.
Methods: We have studied prospectively patients referred under the 2-week waiting time standard (Group I, $n = 25$) with contemporaneous urgent referrals (Group II, $n = 30$), routine referrals deemed urgent by the consultant (Group III, $n = 30$) and routine referrals (Group IV, $n = 50$). We have compared the percentage of malignancies and other serious non-neoplastic diseases as well as the waiting times in the four groups
Results: In Group I, 15 per cent of referrals had proven malignancy and a further 25 per cent had serious non-malignant diseases. The average waiting time was 7 days (range 1–18) and 95 per cent of patients were seen within 2 weeks. In Group II, 8 per cent of referrals had malignancies and 20 per cent had serious non-malignant diseases. The average waiting time was 18 days (range 1–37). In Group III, 15 per cent of referrals had malignancies and 30 per cent had serious non-malignant diseases. The average waiting time was 26 days (range 8–37). In Group IV, 2 per cent had malignancies, and 12 per cent had other serious diseases. The average waiting time was 64 days (range 12–132). The routine waiting time rose by an average of 30 days.
Conclusions: The 2-week waiting time standard is being met at the expense of a substantial increase in the waiting time for routine referrals while not necessarily identifying treatable cases of cancer.

Poster 017

A prospective institutional audit of gastrointestinal anastomotic leak: implications for clinical governance and revalidation

Z.H. Krukowski, M. Turner, E. Pearson and R.A. Keenan
Aberdeen Royal Infirmary & University of Aberdeen, UK

Aims: The Scottish Audit of Surgical Mortality (SASM) has repeatedly identified anastomotic leakage as major adverse factor in surgical deaths. However the lack of a denominator is a criticism of this type of audit and to place a mortality audit in context we performed a prospective analysis of the outcome of all gastrointestinal anastomoses within an institution over a 1-year period. The objective was to establish the feasibility of introducing a monitoring system for this key clinical outcome indicator in a large teaching hospital covering all surgical specialities.
Methods: Surgeons were required to record data on completion of any operation that involved an anastomosis within the GI tract. Completion of the forms was policed by a single senior operating theatre nurse. The forms and a discharge summary were sent to a central audit office. Missing

discharge letters were retrieved by the audit office and clinical questions resolved by scrutiny of the medical record by surgical audit staff

Results: During a 12-month period a total of 522 anastomoses were made in 435 patients during 449 operations. The median age was 65 yrs (range <1–95 yrs) with 222 (51 per cent) females 312 (69 per cent) operations were elective; 61 per cent by consultants and 137 (31 per cent) were non-elective, 74 (54 per cent) by consultants. 35 per cent patients were grades ASA3 or higher, 23 (5 per cent) patients died and 17 (3 per cent) of anastomoses leaked. Eight (47 per cent) patients with leaks died 11 consultants performed one or two anastomoses in 12 months and there was one (7 per cent) leak in this group. Seven surgeons performed more than 30 anastomoses with a 2 7 per cent leak rate (range 0–7 5 per cent).

Conclusion: Medical staff still cannot be relied upon to record data accurately Crude activity and outcome analysis requires risk stratification. The resource implications in terms of facilities, staff and time to provide the meaningful data required for revalidation and clinical governance are substantial

Lower Gastrointestinal

Poster 018

Factors affecting patient outcome with intra-abdominal sarcomas

S MacKenzie and P.J. O'Dwyer

University Department of Surgery, Western Infirmary, Glasgow, UK

Aims: Intra-abdominal sarcomas are rare with approximately 100 new cases occurring annually in the UK The management of these tumours requires a multi-disciplinary approach involving pathology, radiology, clinical oncology and gastrointestinal surgery The aim of this study was to examine the factors that influence patient outcome following treatment for such tumours.

Results: Between January 1990 and October 2000, 117 operations were performed in 102 patients for intra-abdominal, abdominal wall and inguinal soft tissue tumours Eighty-three operations were undertaken for intra-abdominal tumours only. The median age of the group was 49 (IQR 39–58) while 63 per cent of the population were female. Fifty per cent of operations were for recurrence after a primary operation elsewhere. Macroscopic clearance of all tumour was achieved in 78 per cent, while tumour site, size, grade and type was noted for all patients Four patients (5 per cent) died in the postoperative period, two from postoperative bleeding, one from intra-abdominal sepsis and one from a cerebrovascular accident. Patients whose sarcoma arose from the pelvis received either pre- or post-operative radiotherapy Patients with a high-grade irresectable tumour had post-operative chemotherapy. The only significant factor affecting patient survival was whether macroscopic clearance of the tumour was achieved at operation or not. The median survival for patients who had macroscopic clearance of all intra-abdominal tumour was 66 months (range 9–243 months). This compared with a median survival of 3 months (range 2–5 months) for patients undergoing palliative surgery.

Conclusions: These data show that resection of intra-abdominal sarcomas is feasible, and the most important factors affecting outcome is whether macroscopic clearance or tumour can be achieved or not.

Poster 019

Isolated rectal bleeding is an important symptom of colorectal neoplasia

S MacKenzie, R.G Molloy, D Galloway and P.J. O'Dwyer

University Department of Surgery, Western Infirmary of Glasgow, UK

Aims: An understanding of the presenting symptoms of colorectal neoplasia is a prerequisite for effective investigation While previous studies in this area have concentrated only on colorectal carcinoma, ignoring the role of neoplastic polyps, the aim of this study was to establish the relationship between large bowel symptoms and colorectal neoplasia of all types

Methods: Patients referred for the investigation of large bowel symptoms were studied prospectively. Initial investigation involved flexible sigmoidoscopy with barium enema in those <50 years of age and full colonoscopy for those >50 years

Results: Of the 373 patients studied 53 (14 per cent) had neoplasia (carcinoma 13, polyps 40). The association between symptoms and neoplasia is summarized in the table

Symptoms	No patients	No with neoplasia (%)
Bleeding alone	83	18 (22)
Abdominal symptoms	120	16 (13)
Bleeding and abdominal symptoms	12	12 (12)
Anorectal symptoms ± any other symptoms	72	7 (10)
Totals	373	53 (14)

Conclusions: Contrary to previous studies we have found isolated rectal bleeding to be an important symptom of colorectal neoplasia.

Poster 020

The use of Portsmouth Colorectal Cancer Risk database for assessment of patients presenting with lower GI symptoms in Sutton Coldfield

M Mirza, C Stones, S Dodds, A Allan, S. Korsgen, D. Browne and
M A S Chapman

Department of Coloproctology, Good Hope Hospital NHS Trust,
Sutton Coldfield, B75 7RR

Aims: To assess the validity of the database when applied to a different population.

Methods: The Portsmouth database predicts that 80 per cent of patients who have bowel cancer can be detected by investigating the 20 per cent of patients at highest risk. The risk assessment is based on four questions and patient's age

Methods: The questionnaire was completed by the clinicians prospectively in new patients who presented with bowel symptoms to colorectal clinics. The data from December 1999 to August 2000 were collected Risk scoring of individual patients was carried out using the Portsmouth database All cases with diagnosis of cancer were collated.

Results: Data were collected on 522 patients from out patient clinics The incidence of cancer was 8 per cent in this population. 34 cancers have been identified and 28 of these fell in the high-risk group (risk >5 per cent) Therefore, it was possible to identify two-thirds of the cancers by urgently investigating one-third of patients with highest risk scores

Conclusions: This study confirms that the database is valid in a different geographical area and may be a valuable tool for prioritizing the investigations of patients with lower GI symptoms.

Poster 021

Impact of surgery on gracilis muscle blood flow during an electrically stimulated gracilis neosphincter procedure

A.A. Darakhshan, O A. Ogunbiyi, D.Y Artioukh, P J Lunniss and
N.S Williams

Academic Department of Surgery, St Bartholomew's & The Royal London
School of Medicine and Dentistry, London, UK

Aim: Atrophy of the gracilis muscle is a common finding postoperatively, which may impair neosphincter function, and ischaemia may be responsible for this atrophy Thus, our aim was to study blood flow changes during the various stages of surgery

Methods: Laser doppler flowmetry was used to assess blood flow in the distal and proximal segments of the gracilis muscle as well as the main vascular pedicle. Following baseline readings, measurements were taken at each of the above sites after ligation of the distal segmental vessels and mobilization of the muscle, stretch, transposition and electrical stimulation

Results: Nine patients were studied over 17 months. Muscle mobilization resulted in a drop in distal blood flow that was not statistically significant (ns) Stretch of the muscle increased blood flow in both the proximal (ns) and distal segments (mean 69.01, SE 25 01, $P = 0.0281$) Subcutaneous tunnelling of the gracilis during transposition into the perineum reduced blood flow in all regions, significant in the distal segment only (mean −116.4, SE 41 0, $P = 0.0251$). Blood flow increased in all regions with electrical stimulation, but this increase was accentuated distally when the frequency of stimulation was lowered (mean 178.6, SE 76.88, $P = 0.059$).

Conclusions: Mobilization and transposition of the gracilis into the perineum significantly reduced distal muscle blood flow, which could result in ischaemic muscle atrophy and poor neosphincter function Although electrical stimulation was shown to overcome this reduction in perfusion, perioperative stimulation of the muscle is not routinely undertaken due to the risk of sling displacement. These results indicate a reassessment of current practice may be warranted

Poster 022

Emergencies in colorectal cancer

T.T. Irvin, S. Marriott, R. Holbrook and The Multidisciplinary Colorectal Cancer Team

Departments of Surgery and Clinical Audit, Royal Devon & Exeter Hospital (Wonford), Exeter, UK

Aims: Recent studies have suggested that a minority of emergency admissions of patients with colorectal cancer are caused by obstruction or perforation of the primary tumour. The purpose of this prospective study was to determine the reasons for emergency admissions of colorectal cancers and the early outcomes in these patients.
Methods: A consecutive series of 530 patients with colorectal cancer was studied, 166 presenting as emergency admissions. The clinicopathological features of elective and emergency admissions were recorded and analysed in a Dendrite database.
Results: Seventy-nine per cent of emergency admissions were in general surgery and 19 per cent in medical specialties. The reasons for emergency admission included intestinal obstruction (37 per cent), bleeding or anaemia (34 per cent), perforation (8 per cent) and miscellaneous factors (21 per cent). The results of comparative studies of emergency and elective admissions are shown in the table

	Elective (per cent)	Emergency (per cent)	Analysis
ASA grades 3 or 4	33.9	48.0	$P<0.01$
POSSUM mortality prediction > 50 per cent	6.0	12.0	$P<0.01$
Dukes' stage A primary tumour	17.6	5.0	$P<0.001$
Complete excision of primary tumour	75.4	61.8	$P<0.01$
Postoperative complications	17.6	25.9	$P<0.05$
30 day mortality	4.5	10.8	$P<0.01$

Conclusions: Although a minority of emergencies have obstruction or perforation of the tumour the overall prognosis is poor, with a significantly higher incidence of unfit patients, advanced pathology, incomplete tumour excisions and a higher 30-day mortality compared with elective admissions.

Poster 023

Major colorectal cancer resection should not be denied to the elderly patient

J.J. Smith, C. Burke, I.J. Franklin, M. Adams and P.M. Dawson

Colorectal Surgical Unit, West Middlesex University Hospital, Twickenham Road, Isleworth, Middlesex, UK

Objectives: Surgery for colorectal cancer in patients aged over 80 years is often deferred due to the perceived high mortality and morbidity associated with these procedures (NCEPOD). The population is getting older and living longer. Should surgery be denied to this age group based on the above assumption?
Methods: Data were collected on all patients undergoing colorectal cancer resections between January 1994 and July 2000. 276 patients were included, 59 (21.3 per cent) were aged 80 or over (Group I). The mean follow-up period was 46 months in Group I and 53 months in Group II.
Results: There were 80 deaths; 19 (32 per cent) in Group I and 61 (28 per cent) in Group II ($P=0.51$). The 'in-hospital' mortality was 11.9 per cent in Group I and 4.1 per cent in Group II ($P=0.025$). The 5-year survival (all-cause-mortality) in Group I was 64.8 per cent, and 68.9 per cent Group II ($P=0.02$). 47 per cent of deaths in Group I and 63 per cent of deaths in Group II were directly attributable to cancer. Group II had predominantly later stage (Dukes) tumours than Group I ($P=$ ns). Cox regression analysis of all patients identified the following factors to be independently related to overall survival: Age > 80 yrs, post-operative anastomotic leak, increasing Dukes stage, post-operative radiotherapy, and distant recurrence of disease.
Conclusions: There was no significant difference in the number of deaths between the two groups. 'In-hospital mortality' and crude 5-year survival is better (only just) for patients under 80. Whilst age > 80 yrs is an independent risk factor for postoperative mortality, patients should not be denied surgery for colorectal malignancy based on their age, as the outcomes are comparable.

Poster 024

Randomized crossover trial of polyethylene glycol electrolyte solution and water for colostomy irrigation

A. O'Bichere, R.G. Springall, A. Umughete,[1] C. Green and R.K. Phillips

St Mark's Hospital, Harrow, [1]Charing Cross, London UK

Aims: Water is universally recommended for colostomy irrigation, but is largely absorbed by the colon and may result in less efficient expulsion of stool. This study compared the clinical outcome of colonic cleansing with water and polyethylene glycol solution (PEG).
Methods: Forty-one colostomy irrigators were randomly assigned to either water or PEG (1 sachet polyethylene glycol in 1000mls of water). Washout was performed for 1 week using each regimen in a crossover trial. Patients were given questionnaires to record fluid inflow time (FIT), total washout time (TWT), level of discomfort, cramps, leakage episodes, number of stoma pouches used and satisfaction scores with a visual analogue scale (1–10; 1 being poor, and 10 excellent). Summary measures (median, and inter-quartile range-IQR) for each variable was calculated, and a Wilcoxon's test was used to compare the two treatments.
Results: Thirty-three patients (20 women), mean age 55(39–73) years provided 352 irrigation sessions comprising of water (176) and PEG (176). Irrigation was performed every 24, 48 and 72 h by 17, nine and seven patients, respectively. Subjects utilized the following volumes; 500mL (one), 750mL (two), 1000mL (16), 1500mL (11), 2000mL (two), 3500mL (one) but eight failed to complete the study. The median and IQR for water *versus* PEG were: FIT [6 (4.4–10.8) *versus* 6.3 (4.1–11.0); $P=0.48$], TWT [53 (33–69) *versus* 38 (28–55); $P=0.01$], leakage [2.3 (1.7–3.8) *versus* 0.7 (0.2–1.0); $P<0.001$], satisfaction [5.8 (4–7.5) *versus* 8.8 (8.3–10.0); $P<0.001$] and stoma pouch [75 (45–80) *versus* 43 (0–80); $P=0.008$). There was no difference between the two treatments for discomfort and frequency of cramps experienced ($P=0.46$, $P=0.24$, respectively).
Conclusions: PEG performed significantly better than water with shorter washout times, less faecal leakage, higher satisfaction scores and a lower rate of use of stoma bags. It is an effective alternative regimen to water for colostomy irrigation.

Poster 025

COX-2 may act by inducing angiogenesis in colorectal cancer

D. Ghosh,[1] N. Cullen,[3] M. Newbold,[2] A.G. Morris[3] and N. Williams[1]

[1]Department of Surgery and [2]Histopathology, Walsgrave Hospital, Coventry, and [3]Department of Biological Sciences, Warwick University, UK

Aims: Cyclooxygenase-2 (COX-2) expression has been reported to be upregulated in colorectal cancer although its mode of action is yet to be fully elucidated. We investigated the role of COX-2 in stimulating intratumoral angiogenesis.
Methods: Consecutive colorectal cancer specimens were studied by immunohistochemistry for the presence of COX-2. Quantification of COX-2 expression was by a count of the number of positive cells per high-powered field. Angiogenesis was assessed immunohistochemically using a specific antibody (CD31). Data analysis was by simple linear regression.
Results: COX-2 was expressed in all tumours studied. There was a strong positive relationship between COX-2 expression and the magnitude of intratumoral angiogenesis ($R^2=0.71$, $P<0.01$).
Conclusions: COX-2 is expressed and up-regulated in colorectal cancer. It may exert its effect by acting as a proangiogenetic factor, thereby supporting tumour growth and progression.

Poster 026

Abnormal P-cadherin and altered expression of B-catenin in ulcerative colitis associated dysplasia and colorectal cancer

A.I. Haq,[1] J. Jankowski,[1,2] M.C. Winslet,[1] D. Morton[2] and O. Ogunbiyi[1]

Royal Free and [1]UCL Medical Schools and the Department of Surgery at the [2]University of Birmingham, UK

Aims: The cell adhesion protein, P-cadherin is known to be abnormally expressed in ulcerative (UC) and Crohn's (Cr) colitis. Our aim was to determine whether placental (P) cadherin and β-catenin was aberrantly expressed in UC dysplastic and neoplastic lesions (UCCRC).
Methods: Archival paraffin-embedded sections consisted of the following: 18 UCCRC (six well; eight moderately and four poorly differentiated adenocarcinomas) and nine dysplastic lesions. Immunohistochemistry was carried out using P-cadherin and β-catenin. The distribution of P-cadherin

and β-catenin was classified according to their distribution in the nuclei, cell membrane or cytoplasm.

Results: P-cadherin and β-catenin were expressed in the cytoplasm and basal cell membrane of all the dysplastic, well and moderately differentiated carcinomas. There was no expression in the poorly differentiated carcinomas. There was nuclear expression of β-catenin in two well and two moderately differentiated carcinomas.

Conclusions: Aberrant P-cadherin is associated with UCCRC and dysplasia, and is seen in the absence of β-catenin nuclear translocation. Interestingly, both these features are absent in poorly differentiated tumours Although the numbers are small, this might indicate a specific role for P-cadherin in early UC-related neoplasia.

Poster 027

Long-term results of laparoscopic surgery for colorectal cancer

H. Hasegawa, M. Watanabe and M. Kitajima

Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Aims: To analyse long-term results of laparoscopic surgery in patients with colorectal cancer.

Methods: Between June 1992 and August 2000, 346 patients with colorectal cancer (212 men and 134 women, mean age 62 0 years) underwent laparoscopic surgery. The median follow-up was 36 months (range 2 – 103 months) Five-year survival rates were calculated using a Kaplan–Meier method.

Results: Sites of tumour were distributed in the caecum: 41 (12 per cent), ascending 62 (18 per cent), transverse: 58 (17 per cent), descending: 16 (5 per cent), sigmoid: 116 (33 per cent) and the rectum: 53 (15 per cent) As for the local invasion, there were 105 (30 per cent) pTis, 116 (34 per cent) pT2, 58 (17 per cent) pT3 and three (1 per cent) pT4 tumours Clinicopathological staging identified 257 patients (74 per cent) with Dukes' A, 41 (12 per cent) with B, 43 (12 per cent) with C and five (1 per cent) with Dukes' D. Postoperative complications included wound sepsis in 16 patients (4 6 per cent), anastomotic leakage in 12 (3 5 per cent) and bowel obstruction in six (1.7 per cent) Of 341 curative cases, eight patients developed recurrences (liver, five; peritoneum, four) The 5-year survival rate was 97.9 per cent for Dukes' A, 92.5 per cent (maximum 4 years) for Dukes' B and 82.2 per cent for Dukes' C

Conclusions: Laparoscopic surgery for colorectal cancer is feasible with favourable long-term results, but further follow-up is necessary.

Poster 028

Minimally invasive ileo-caecal and ileocolic resection for Crohn's disease – a seven-year experience

A. Willis, S Kardirkamanathan, N. Gallegos and R.W Motson

Colchester General Hospital, Turner Road, Colchester, Essex C04 5JL, UK

Methods: Analysis of a prospectively maintained laparoscopic database was undertaken Fifty four patients (18 males and 36 females) with median age of 35 years underwent laparoscopically assisted surgery for Crohn's disease. All had Crohn's disease preoperatively confirmed radiologically, and had undergone medical therapy including steroids, but had failed to respond or had relapsed Median duration of symptoms between diagnosis and operation was 38 months (range 0–420). Thirty (54 per cent) had undergone previous abdominal surgery and 18 (32 per cent) had previous surgery for Crohn's Disease

Results: Fifty-six operations were undertaken, 32 ileocaecal resections and 24 ileocolic resections. Seven (12 3 per cent) were converted to open surgery. There were no deaths Three major complications occurred and required laparotomy (small bowel obstruction, anastomotic leak and ileo-colic fistula) In the laparoscopically assisted group, the median hospital stay was 5 days (range 2–24) and median time to full activity was 21 days (range 6–159). Median follow-up after surgery was 18 months (range 1–74), 39 remained symptom-free and eight had minimal symptoms, but no clinical or radiological evidence of recurrence of Crohn's disease Eight subsequently presented with recurrent disease requiring further medical ($n = 5$) or surgical ($n = 3$) treatment

Conclusions: Laparoscopically assisted resection is safe in the majority of patients with ileocolic or ileocaecal Crohn's disease.

Poster 029

Outcome of anal fistula surgery in Crohn's disease

M R B Keighley and E Mylonakis

University Department of Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

Aims: We have prospectively studied the results of operations for symptomatic anorectal fistulas (AF) in Crohn's disease (CD)

Methods: Thirty patients with 37 AF and CD were studied clinically and using a continence score and anorectal physiological studies before and three months after operation; 18 women, mean age 37 8 (range 25–53 years) Three of 37 AF were superficial, 13 of 37 were intersphincteric, 20 of 37 were trans-sphincteric and 1 of 37 supersphincteric Thirteen AF were laid open and 24 were treated by a loose seton Follow-up was 2.1 years (range 0.8–2 6).

Results: In patients managed by lay-open, continence status deteriorated significantly; Cleveland Incontinence Score (CIS) deteriorated from 5 3 to 10 4 ($P = 0.0004$); resting and squeeze anal pressures fell from 58.2 to 36 3 and from 78.3 to 59 6, respectively ($P = 0.006$ and $P = 0\ 01$). The volume of first leakage also fell from 529 6 mL to 312.7 mL. After loose seton, the CIS deteriorated only slightly from 4 2 to 7.1 (P = 0 03), resting and squeeze pressures also fell from 50 2 to 43.2 and from 76 8 to 68 0, respectively ($P = 0.02$ and $P = 0.02$) The volume of first leakage fell from 512 1 mL to 398 2 mL During the study period 22 of 30 AF healed in a mean time of 4 7 months (3.2–7.1)

Conclusions: Laying open and AF in CD compromises continence more than the use of a loose seton Furthermore, surgical treatment achieves healing in only three-quarters of all patients

Poster 030

Closed lateral subcutaneous sphincterotomy under direct endosonographic control

E Mylonakis, D.G Morton, S Radley and M R.B. Keighley

University Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK

Aims: Closed lateral subcutaneous sphincterotomy (CLSS) is the procedure of choice for chronic anal fissure because healing rates are high but there is a small risk of transient or permanent impaired continence This study was undertaken to determine if CLSS under direct endosonographic control (CLSSEC) is more effective and safer than standard CLSS

Methods: Thirty patients had CLSSEC and 20 had CLSS The groups were comparable for age, sex and duration of follow-up. All patients underwent clinical and anorectal physiological evaluation before and 3 months after the operation. Endoanal ultrasonography was used before and after the operation to assess the completeness of sphincterotomy.

Results: Fissures healed in all CLSSEC patients, whereas two persisted or recurred after CLSS. Impaired continence to flatus or soiling at 1 month was observed in seven (23 per cent) after CLSSEC compared with four (20 per cent) after CLSS Only one, a CLSSEC patient, had persistent impaired continence at 3 months Ultrasound revealed a complete internal sphincter defect in all CLSSEC patients but in only four of 10 in the CLSS group The fall in resting pressure was greater after CLSSEC; 98.4 ± 31.2–63 1 ± 19 4, $P = 0.02$ than after CLSS, 94 9 ± 27 3–76.5 ± 20 1, ns

Conclusions: These data indicate that CLSSEC is a more precise method of sphincterotomy but does not eliminate the risk of transient or even permanent impaired continence

Poster 031

GTN and diltiazem have an additive effect on isolated sheep internal anal sphincter

M. Jonas, J H Scholefield and V G Wilson

University Hospital, Queen's Medical Centre, Nottingham, UK

Aims: Topical GTN (nitric oxide donor) and diltiazem (calcium-channel blocker) lower internal anal sphincter (IAS) tone GTN heals two-thirds of chronic anal fissures, but many patients experience troublesome headaches In combination, acting via different pathways, these drugs may have an additive effect and allow lower doses of each to be used, possibly reducing side-effects

Methods: Isolated strips of sheep IAS (previously validated as a model for human IAS), developed spontaneous myogenic tone in response to application of isometric tension. A maximal concentration of GTN (obtained from cumulative concentration response curves) was added, followed by diltiazem once steady-state conditions were achieved, the drugs

were also added in reverse order, and experiments repeated in IAS from six sheep.
Results: Maximal concentrations of GTN and diltiazem each decreased sheep IAS tone by approximately 70 per cent. GTN initially caused a 95 per cent reduction in IAS tone within 2 min, but there followed some recovery of tone to a steady state after 10min. Diltiazem took 10 min to reach maximal effect, but this effect was sustained. The combined effect of GTN and diltiazem was complete abolition of IAS tone irrespective of the order in which they were added.
Conclusions: GTN and diltiazem have an additive effect on sheep IAS tone. A combination of these drugs may improve both efficacy and acceptability of treatment for chronic anal fissure.

Poster 032

Systemic levels of GTN following topical application do not correlate with the reduction in anal pressure

M. Jonas, K.R. Neal, D. Barrett and J.H. Scholefield
University Hospital, Queen's Medical Centre, Nottingham, UK

Aims: Topical 0.2 per cent GTN lowers resting anal pressure (RAP) and heals two-thirds of chronic anal fissures. Over 50 per cent of patients experience headaches, presumably through systemic absorption, but the pharmacokinetics of GTN are unknown. This study evaluated the systemic absorption profile of GTN, and correlation with RAP, haemodynamic parameters and side-effects.
Methods: Thirty healthy volunteers underwent continuous static anal manometry 10 min before and 2 h after application of 0.2 per cent GTN (0.5 g) ointment to the anoderm. Blood samples were taken from an intravenous cannula, pulse and BP measured pre-GTN, and 10, 20, 30, 40, 50, 60, 90, 120 and 180 min post-GTN. Side-effects were recorded.
Results: GTN was detected in the plasma 10min to 3 h after topical application. RAP was significantly reduced after 10 min, but had returned to pre-treatment values by 120 min. Pulse was statistically unchanged during the study; systolic BP was significantly lower 20–90 min post-GTN, and diastolic BP throughout the study. There was no correlation between plasma GTN concentration, RAP, and the onset, duration or intensity of headaches.
Conclusions: Topical GTN acts locally on the IAS; systemic levels do not contribute significantly to the reduction in RAP. There is marked inter-individual variation between plasma GTN levels, and no correlation with haemodynamic parameters and side-effects.

Poster 033

A randomized controlled trial of stapled *versus* diathermy haemorrhoidectomy

M.J. Cheetham, C.R.G. Cohen, M.A. Kamm and R.K.S. Phillips
St Mark's Hospital, Watford Road, Harrow, UK

Aims: Stapled haemorrhoidectomy is believed to be less painful than conventional haemorrhoidectomy and should allow an earlier return to work. We aimed to compare stapled haemorrhoidectomy with diathermy haemorrhoidectomy.
Methods: Thirty-one patients were randomized to undergo diathermy haemorrhoidectomy ($n = 16$) or stapled haemorrhoidectomy performed with a purpose-designed endoluminal stapling device ($n = 15$). All operations were performed under general anaesthetic in the lithotomy position. Patients received a standard package of care including lactulose (commenced preoperatively), post-operative oral metronidazole, GTN ointment, diclofenac and codydramol. They were assessed by structured interview to assess their symptoms before and after surgery. Patients completed a 10cm visual analogue scale daily for the first 10 days after surgery to determine pain scores.
Results: The total pain score (sum of all pain scores) was significantly higher in the diathermy group (50.0 (9.8–79.9) *versus* 19.6 (1.3 – 89.5), $P = 0.03$). Patients took a median of 14 days (range 3–21) off work after diathermy haemorrhoidectomy compared with 10 days (range 3–38) for the patients undergoing stapled haemorrhoidectomy ($P = 0.15$). At long-term follow up, three patients (all in the stapled group) developed new symptoms of faecal urgency and anal pain and three patients required further surgery to remove symptomatic external haemorrhoids after stapled haemorrhoidectomy.
Conclusions: Although stapled haemorrhoidectomy is less painful in the short term, this does not lead to a significantly earlier return to work. There is a high incidence of new and residual symptoms at long-term follow-up.

Poster 034

Audit of perineal wound healing after primary closure of the perineal wound without perineal drainage in abdominal perineal resection for malignancy

E.P. Weledji and J. Palmer
Cumberland Infirmary, Carlisle, UK

Aims: This study reports the results of primary closure 'sealing' of the perineum following abdominal perineal excision for malignancy, irrespective of risk factors (pre-operative radiotherapy, age, advanced malignancy, diabetes mellitus, inadequate haemostasis).
Methods: Seventy-four consecutive patients (48 males, 26 females, median age 70 years) with rectal carcinoma (72) and anal carcinoma (two) from August 1989 to December 1999 were identified retrospectively. Data from individual patients' case notes were recorded: age, sex, stage of tumour, pre- or post-operative radiotherapy, perioperative risk factors (faecal contamination, locally advanced tumour, haematoma) and co-morbidity. Complications of the perineal wound were tabulated as: (1) cellulitis; (2) suppuration; (3) haematoma; (4) serious collection; and (5) dehiscence. The length of hospital stay and late complications: delayed wound healing, perineal sinus and perineal hernia, were recorded.
Results: Fifty-five of 74 patients (75 per cent) healed primarily by 3 weeks and delayed healing occurred in 19 (25 per cent) patients including three (4 per cent) with complete dehiscence. Four of nine patients (45 per cent) who received pre-operative radiotherapy achieved primary healing and five (55 per cent) patients delayed healing. Two of 36 patients (6 per cent) who received post-operative radiotherapy developed wound complications. 35 per cent of the primarily healed group had Dukes' B disease as compared to 55 per cent of the delayed healing group. 60 per cent of the dehiscence sub-group had stage B disease. Primary healing occurred in 69 per cent of males and 85 per cent of females; delayed healing in 31 per cent of males and 15 of females. We were unable to relate failure of primary closure to the patient's age, weight, serum albumin or haemoglobin. The average length of hospital stay following primary healing was 12.25 days and 17.05 days following delayed healing.
Conclusions: A technique of complete primary closure of the perineal wound by obliterating the perineal dead space over a transabdominal suction drain can provide a primary healing rate of 75 per cent by 3 weeks irrespective of risk factors. The locally advanced and fixed Dukes' B rectal carcinoma have been observed to have a significant effect on the delayed healing rate.

Poster 035

How good is sexual function after rectal surgery?

P. Mackey, L. Bevan, J. Beynon and N.D. Carr
Department of Colorectal Surgery, Singleton Hospital, Swansea, Wales, UK

Aims: Impotence and retrograde ejaculation are recognized complications of rectal surgery, but less information exists concerning the wider issues of sexual dysfunction, particularly in females. The present study examines sexual outcome in terms of body image, level of desire, sexual satisfaction and the effect of surgery on patients and their partners after rectal excision.
Methods: Patients were randomly selected from a database and were requested to complete a postal questionnaire.
Results: Twenty-four males and 23 females (median age 69, range 18–85) were sent the questionnaire. 54 per cent of males and 39 per cent of females responded and all were in a relationship. The results indicated that both sexes were affected by decreased body image, but as might be expected this was higher in females (55 per cent *versus* 21 per cent). The level of sexual desire was reduced in 38 per cent of males and 44 per cent of females after surgery. Interestingly, 66 per cent of females and 38 per cent of males reported that surgery had an adverse effect on their partners. 54 per cent and 67 per cent of males and females, respectively, experienced sexual satisfaction postoperatively. Only 31 per cent of males and 33 per cent off females reported that they had been warned of possible postoperative sexual malfunction prior to operation. Outcome was independent of the presence of a stoma.
Conclusions: The results of this study indicate that a variety of sexual problems exist after rectal excision and that more extensive preoperative counselling is required.

Poster 036

Phantom rectum following rectal excision

R.D Church, M Claridge and R Hutchinson

Stafford District General Hospital, Weston Road, Stafford, UK

Aims: Phantom rectum is the sensation of a normal rectum after anorectal excision. The aims of the study were to determine the prevalence of phantom sensations, correlations with indications for surgery, stage of disease, effects of adjuvant therapies.

Methods: Patients who had undergone anorectal excision between October 1996 and December 1999 were identified. 37 surviving patients were interviewed using a standard questionnaire. The patients were asked if they had various sensations of phantom rectum, such as sensation of desire to defecate or pass flatus. The time of onset frequency and the nature of any resolution were noted. Case notes were reviewed for relevant clinical information. This included nature of the operation, indication for surgery, type of dissection and postoperative recovery and any adjuvant therapies.

Results: Seventy-two per cent of patients had symptoms of phantom rectum. Men were statistically more likely to suffer with symptoms of phantom rectum when compared with the women. Panproctocolectomy patients were also more likely to suffer. Onset of symptoms occurred early and tended to resolve spontaneously in 50 per cent of patients. The symptoms or the history of symptoms bore no relation to other pathophysiological characteristics such as nature of disease or adjuvant therapies. Symptoms were often mild, caused little distress and tended to resolve spontaneously. However some patients reported a degree of distress and anxiety related to these sensations.

Conclusions: We concluded that phantom rectum is common but symptoms are mild and patients can be reassured. Pre- and post-operative counselling of phantom sensations and pain should be routine.

Poster 037

Treatment of chronic constipation and faecal leakage with an antegrade continence enema (ACE) procedure improves quality of life

R P Baker, J Marshall, P Neary, M.A Ismail and G S Duthie

Academic Surgical Unit, Castle Hill Hospital, Hull, UK

Aims: We describe our experience of 10 adults who have undergone this procedure and compare quality of life scores in pre- and post-operative patients.

Methods: A retrospective review from case notes and stoma care nurse records of the patients who have had an ACE procedure. Quality of life was assessed in postoperative patients with the verified SF-36 form and compared to a similar cohort of patients awaiting the procedure.

Results: Ten patients (eight female), mean age 29 years, have undergone the procedure seven laparoscopically, six suffered with chronic constipation, three with faecal leakage and one a mixed picture. All recovered well postoperatively with no surgical complications, minor technical difficulties with the irrigation procedure are common and have lead to readmission. Two had minor revision surgery of the stoma and four stricturoplasties, one became constipated again due to irrigation difficulties and required inpatient aperients. QOL comparisons showed significant improvement in the mean mental component score of the SF-36 form from 32.3 to 49.0 ($P = 0.038$) and an improvement albeit not statistically significant in the mean physical component score from 36.28 to 43.3 ($P = 0.133$).

Conclusions: The antegrade continence enema procedure is technically simple and effective in the treatment of adults with chronic constipation and faecal leakage. Patients who have had the procedure demonstrate a significant improvement in the mean mental component score of the SF-36 QOL assessment compared with a similar cohort of patients awaiting the procedure.

Transplantation

Poster 038

Measuring intrarenal vascular resistance during machine perfusion preservation does not improve upon the assessment of renal viability made on clinical grounds

M S Metcalfe, R N Saunders, S A. White, G J. Murphy, T Horsburgh, P S Veitch and M L Nicholson

Transplant Division, University Department of Surgery, Leicester General Hospital, UK

Aims: A reliable objective test of the viability of ischaemically damaged kidneys prior to transplantation would be very valuable in assessing organs from an uncontrolled non-heart-beating donor (NHBD). Currently in Leicester, viability assessment in such instances is made using the estimated warm ischaemic time and the macroscopic appearances of the kidney at retrieval. The aim of this study was to assess the potential of intrarenal vascular resistance measurements during hypothermic machine perfusion preservation to determine renal viability.

Methods: Seven pairs of uncontrolled NHBD kidneys were determined at the time of harvesting to be fit (group 1) or unfit (group 2) for transplantation according to their appearances as assessed by the retrieving surgeon. This decision was adhered to irrespective of the results of machine perfusion. All 14 kidneys were then perfused with hyperosmolar citrate solution on a Waters RM3 unit at a systolic pressure of 60 mmHg and a temperature of 3–7°C for 6 h. The intrarenal vascular resistance was recorded throughout the perfusion, and the values at the beginning were compared. Statistical analysis was by the Mann–Whitney U-test and Spearman's rank correlation.

Results: Eight kidneys were allocated at retrieval to group 1, and 6 to group 2. Of the eight kidneys transplanted, five functioned after a delay (group 1a) and three never functioned (group 1b). The median initial resistance for group 1a was 0.70 ($\text{mL min}^{-1}\ \text{mmHg}^{-1}\ 100\text{g}^{-1}$), 0.67 for group 1b, and 1.32 for group 2 ($P = 0.003$). In those kidneys that did function there was no significant correlation between best serum creatinine and initial renal vascular resistance ($P = 0.6$).

Conclusions: Intrarenal vascular resistance during machine perfusion is higher in kidneys that are macroscopically unfit for transplantation. However, intrarenal resistance does not help in the distinction between viable and non-viable organs in those judged macroscopically to be fit for transplantation.

Poster 039

Normothermic preservation of donor livers

C J Imber, S D St Peter, I Lopez, D Piggott, J. Mcguire, D Hughes and P J Friend

Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK

Aims: We propose to develop a means of preserving donor livers whereby the organ is perfused with blood and maintained at normal body temperature. The liver will, therefore, continue to function during preservation and it is proposed that this will prevent both the progressive decline in organ viability and the ischaemia-reperfusion injury associated with cold preservation, and allow a method to assess viability prior to transplantation.

Methods: Porcine livers were retrieved from a donor animal and cold flush preserved in UW solution for 24 h, or perfused normothermically with allogeneic blood on an extracorporeal circuit utilizing paediatric cardiopulmonary bypass technology. Both groups then underwent a 24-h reperfusion phase utilizing the circuit as a surrogate for transplantation, and perfusate, bile and liver biopsies analysed as markers of subsequent organ viability.

Results: Organs preserved normothermically on an extracorporeal perfusion circuit displayed superior liver function in terms of synthetic (factor V, bile production), metabolic (galactose elimination kinetics, glucose utilization, acid/base homeostasis) and haemodynamic (total flow, hepatic artery resistance) parameters. Significantly ($P < 0.05$) less global liver (transaminase release), structural damage (histology) and reperfusion injury (kupffer cell damage, immunohistochemistry) was identified in the warm preserved group.

Conclusions: Normothermic machine perfusion offers an optimal preservation technique when compared with traditional cold flush. It also offers the ability to assess organ viability prior to transplantation, so optimizing the utilization of an extremely scarce and precious commodity.

Vascular

Poster 040

155 vascular injuries, a retrospective study (1992–2000)

S.K. Asfar, J. Al-Ali, H.A. Gafar, H. Safar, A. Gawish and M. Al-Bader

Depatment of Surgery, Mubarak Al-Kabeer Hospital, Kuwait

Aims: To audit our experience in management of vascular trauma between 1992 and 2000.

Methods: Retrospective review of all patients treated for vascular trauma.

Results: One hundred and fifty-five patients with vascular injuries were managed during the period 1992–2000. 30.3 per cent ($n = 47$) were stab wounds and 23.3 per cent ($n = 36$) were due to RTA. 21 neck injuries (13.5 per cent), six chest injuries and 10 patients with abdominal vascular injuries. Of the latter, three patients died on the operating table because of exanguination. 118 patients had limb injuries. 49 (32 per cent) were upper limb and 69 (44.5 per cent) were lower limb injuries. Of the latter, two patients presented with bilateral crush injuries, revascularization of only one limb was performed in each case. The other limb was severely traumatized beyond repair. Autogenous vein was used in the majority of cases for revascularization. All 49 upper limb revascularization were successful. Of the 69 revascularized lower limbs, four grafts failed: two within 24 h due to poor run-off and extensive soft tissue loss, respectively, the other two failed after 6 months due to progressive atherosclerosis, HTN, DM and Buerger's disease, respectively. One patient died on the tenth postoperative day due to PE with patent graft. The long-term patency rate of revascularized limbs at a median follow up of (4.4 ± 2 years) was 96 per cent. The amputation rate was 1.3 per cent and the mortality rate of all vascular traumas in this report was 2.5 per cent.

Conclusions: The use of autogenous vein graft is associated with good results. Progression of peripheral vascular disease and diabetes are risk factors for graft failure.

Posters 041

Does renal artery intervention confer any benefit in patients with bilateral atherosclerotic renal artery stenosis?

W.R. Pillay, J.N. Crinnion, A.A.B. Barros D'Sa† and J.H.N. Wolfe

Regional Vascular Unit, St Mary's Hospital, London, UK and †The Royal Victoria Hospital, Belfast, UK for the Joint Vascular Research Group

Aims: The natural history of bilateral atherosclerotic renal artery stenosis (ARAS) is unpredictable. We have investigated whether intervention results in improved renal function and fewer cases of progressive renal failure.

Methods: Thirty-three patients with peripheral vascular disease and co-existing significant bilateral ARAS (stenosis > 50 per cent) were enrolled in a multicentre prospective study. Baseline measurements of serum creatinine, renal size and diastolic blood pressure were recorded and repeated at six-monthly follow-up. The follow-up period ranges from 2 to 4 years (mean 2.4). Those patients who underwent revascularization (Group 1, $n = 12$) were compared to those managed conservatively (Group 2, $n = 21$). 13 endovascular procedures (4 bilateral) and 3 open operations were performed

Results: These are shown in the table as median (interquartile range).

	Group 1	Group 2	Total
Number	12	21	33
Mortality (%)	4 (33%)	6 (29%)	10 (30%)
Dialysis	1 (died)	0	1 (died)
Creatinine			
Baseline	140 (122–238)	108 (90–166)	119 (96–205)
Follow up	189 (132–233)	105 (98–155)	117 (100–189)
BP			
Baseline	90 (80–100)	85 (73–90)	90 (75–95)
Follow-up	77 (68–82)	80 (70–85)	80 (70–85)

Nearly one-third of patients died in both groups but this was not directly attributable to renal failure. Four patients who had undergone intervention had contralateral occlusion. Of these, three died within the follow-up period, one after becoming dialysis-dependent (creatinine 746 μmol L^{-1}). Follow-up creatinine in the intervention group was significantly higher than baseline (Wilcoxon signed rank test for paired observations, $P = 0.04$). At 2-year follow-up, 6/9 surviving patients following intervention had a > 15 per cent decrease in renal function, whereas this occurred in 5/15 of those with no intervention. Renal size measured on ultrasound was unhelpful due to the inter-observer variability in measurements.

Conclusions: Bilateral ARAS has a poor prognosis; the majority of deaths are not related to the renovascular disease. Despite the mortality rates being similar in both groups, deterioration in renal function was significant only in those undergoing intervention.

Poster 042

Auditing ultrasound accuracy for abdominal aortic aneurysm (AAA) screening

M.J. Forshaw,[1] A.B.M. Wilmink,[1] C.S.F.F. Hubbard,[2] N.E. Day[3] and C.R.G. Quick[1]

Departments of [1]General Surgery and [2]Radiology, Hinchingbrooke Hospital, Huntingdon, and [3]Institute of Public Health, University of Cambridge, Cambridge, UK

Aims: Within a long-running AAA screening project, ultrasound measurements need to be consistent and reproducible to justify clinical decision making. This study has audited the accuracy of ultrasound (US) as a screening tool and correlated US measurements of infrarenal aortic diameter (IAD) with computerized tomography (CT); interobserver measurement variability was also assessed.

Methods: Over 12000 ultrasound scans have been performed by nine ultrasonographers since 1991 in a community based AAA screening program in the Huntingdon district. The maximum IAD was measured in the anteroposterior plane using a Toshiba Capasee with a 3.5 MHz curvilinear probe. An AAA was defined if the maximum IAD was greater than 29 mm. CT was then performed if the IAD is greater than 45 mm and again the IAD recorded. The false negative rate was calculated from the number of normal ultrasound scans in patients with a ruptured AAA who had been screened. The false positive rate was calculated from the number of aneurysmal aortas on US that were subsequently classified as normal on CT.

Measurement: Variability between CT and US and between observers were calculated using a 'limits of agreement' method.

Results: Only 11 out of 80 patients with a ruptured AAA since 1991 had attended screening; all had previous US measurements greater than 29 mm. 64 screened patients with US measurements greater than 45 mm underwent CT: this confirmed the presence of an AAA in all cases. The sensitivity and specificity for ultrasound can both therefore be estimated to be close to 100 per cent. The median time gap between CT and US was 3 months (range, 18–50 months) with a mean difference of 3.8 mm. CT measurements tended to be slightly larger on average. Given that the majority of aneurysms increase in size with time, there was a good correlation ($r = 0.54$) between the time gap of these scans and the measurement differences; this time gap predicted 33 per cent of the measurement differences between CT and US in a linear regression model. The time gap between CT and US was less than 6 months in 52 patients and these patients were used to assess measurement variability between CT and US and between observers (see table).

	US	CT	CT-US (mm)	Limits of variability (mm)
Ultrasonographer 1	6735	36	3.9	−3–8
Ultrasonographer 2	1265	8	3.4	−8–15
Others (7)	4484	8	2.6	−10–16
Total	12884	52	3.6	−5–12

Conclusions: These results confirm that US is an accurate screening test for AAA with a high sensitivity and specificity and can therefore be used for clinical decision making. Discrepancies in measurement between CT and US can, in part, be attributed to the time gap between these scans, but the measurement variability between CT and US and between observers are within acceptable limits.

Poster 043

An intensive care unit bed is not essential for elective aortic aneurysm repair

B. Braithwaite, M. Shaw and R. Nash

Derbyshire Royal Infirmary, Derbyshire, UK

Aims: Cancellation of elective operations for lack of an intensive care bed is an increasingly common problem. The aim of this study was to retrospectively review patients who had an elective AAA repair by a single vascular surgeon.

Methods: Patients were routinely given a thoracic epidural and were maintained under general anaesthesia with a laryngeal mask. Post-operative care facilities comprised a four-bed high-dependency unit (HDU) and a four-bed intensive care unit (ITU) staffed by junior doctors with consultant supervision. Between October 1995 and October 1999, some 98 patients (eight women), median age 71 years (range 57–85) had an elective repair of an infra-renal AAA. The median size of the aneurysm on ultrasound examination was 6.2 cm (range 4.4–10) All but one patient had a thoracic epidural Some 84 operations were done by the consultant surgeon, the remainder by a higher surgical trainee Some 20 grafts were bifurcated, the median operating time was 1 5 h (range 1–3 5) and estimated blood loss was 1000 mL (100–6500). All but eight patients were extubated before leaving the operating theatre. Some 89 patients were transferred for post-operative care in HDU, nine required inotropic support and were managed on the ITU, of these two were predicted to require an ITU bed (one was obese and the other had chronic airway disease) Of the remainder, two had post-operative haemorrhage that required a second laparotomy and one had a peri-operative MI. The median stay on HDU or ITU was 1 day (0–14) and patients were discharged from hospital at a median of 10 days (6–29).

Results: The peri-operative mortality rate was 5 per cent. Five patients died of renal failure (one), exacerbation of chronic airways disease (one), cardiac failure (one) and per-operative myocardial infarction (two) There were 22 non-fatal complications in 18 patients post-operative haemorrhage (two), pneumonia (7, of which one required ITU care after discharge to the ward), temporary renal failure (three), MI (three), arrhythmia (two), prolonged ileus (one), LVF (one) wound dehiscence (one), *C difficile* diarrhoea, and stroke (one)

Conclusions: In this series, only seven patients required unplanned admission to an intensive care bed The combination of epidural assisted anaesthesia, short surgical time and a high-dependency unit can avoid the use of a precious intensive care bed

Poster 044

Is division of the left renal vein during emergency abdominal aortic aneurysm surgery a safe strategy? A North-East of Scotland experience

P. Bachoo, Y Abu-Omar, G. Cooper, J Engeset and K S Cross
Department of Vascular Surgery, Aberdeen Royal Infirmary, UK

Aims: We report our experience of dividing the left renal vein (LRV) during emergency abdominal aortic aneurysm (AAA) surgery and consider the impact of this manoeuvre on renal function at intermediate follow-up

Methods: Clinical, operative and biochemical details of all cases undergoing surgical repair of AAA between 1991 and 1999 were reviewed. Renal function (blood urea/serum creatinine) was compared in cases with (group 1) and without (group 2) LRV division after elective and emergency surgery. Cases were included if renal function was possible at least 1 month after discharge. Indexed case notes were reviewed for data concerning total aortic cross clamp time, recorded blood loss, survival and long-term requirement for renal replacement therapy

Results: Between 1991 and 1999, 30 of 509 cases (5.8 per cent) underwent division of the LRV. In 141 cases data was complete and is presented (male 116, median age 72.6 years, range 55–89 years) Nine cases (all emergencies) from group 1 were excluded: two on-table deaths, five postoperative deaths (CVA two, MRSA septicaemia-one, MOF two), for two, case notes were not available Following discharge renal function was available at 20/19 months for elective/emergency cases, with the results summarized in the table and shown as mean (SEM).

	Elective		Emergency	
Preoperative				
BUN mmol L^{-1}	6 6 (0 38)		9 5 (0 67)	
Creatinine μmol L^{-1}	115 (4 9)		146 (9 2)	
Postoperative	Group 1 ($n=11$)	Group 2 ($n=65$)	Group 1 ($n=10$)	Group 2 ($n=55$)
BUN (mmol L^{-1})	7 7 (1 5)	7 1 (0 4)	13 (2 9)	12 8 (2 6)
Creatinine (μmol L^{-1})	117 (17 4)	119 (5 2)	220 (42 3)	170 (17 7)

Overall, a statistically significant difference ($P=0.001$) in preoperative renal function was observed between elective and emergency cases but within each group dividing the LRV did not cause a statistically significant deterioration in renal function. Mean estimated blood loss, total loss clamp time and survival were similar, group 1. 2.0 L, 71 min, 40 months and group 2: 2.0 L, 85 min, 29 months At follow-up, four patients, all group 2, were receiving renal replacement therapy.

Conclusions: We conclude division of the LRV during emergency AAA surgery is a useful strategy and does not adversely effect renal function at follow-up.

Poster 045

The proximal aortic neck following endovascular aortic repair: a cause for concern?

S.J. Holtham, S. Dugdill, J. Rose, T A Lees and M G. Wyatt
Northern Vascular Centre, Freeman Hospital, Newcastle upon Tyne, UK

Aims: Endovascular aortic repair (EVAR) depends on a stable fixation at the proximal neck of the aneurysm to result in a durable repair. The aim of this study was determine whether the proximal neck continues to expand following EVAR

Methods: EVAR has been performed in 135 patients between December 1995 and August 2000 Follow-up has been performed according to the Eurostar criteria with contrast enhanced CT scans and measurement of the proximal aortic neck at a level distal to the renal arteries.

Results: Of the 135 patients, 36 had completed follow-up to 24 months. Of these patients, the mean pre-operative aneurysm diameter was 59 5±13.5 mm and the mean pre-operative proximal neck diameter was 21 7±1.5 mm At 1 month, the mean proximal diameter was 21 5±1 9 mm (NS) At 6 months follow-up, the mean proximal neck diameter had increased by 1 2 mm from the 1-month measurement ($P=0.004$) At 24 months the mean neck diameter had increased by a further 1.1 mm from the 6-month measurement ($P=0\ 01$) There have been four graft migrations out of 135 patients (3 per cent) with a mean onset of 18 months The mean increase in proximal neck diameter in these patients was 4.5±3 1 mm.

Conclusions: There appears to be an initial rapid increase in proximal neck diameter following EVAR. After the initial 6 months, this increase continues but at a slower rate of 0.8 mm per year This expansion is ongoing and raises the question of the stability of the proximal neck fixation This may bring in to doubt the long-term durability of devices that are fixed in the infrarenal aortic segment

Poster 046

Surgical management of upper limb ischaemia: a 12-year experience

A Mahmood, R. Salaman, M. Sintler, J. Luscombe, M.H. Simms, S R G. Smith, A. Edwards and R.K. Vohra

University Hospital, Birmingham, UK

Aims: The aim was to assess the diversity and aetiology as well as to evaluate the management, outcome and morbidity of upper limb ischaemia.

Methods: A retrospective analysis of all patients admitted to the University Hospital Birmingham NHS Trust with upper limb ischaemia between 1988 and 2000 was carried out. A standard proforma was used to record presentation, aetiology/pathology, treatment and outcome along with routine clinical and demographic data.

Results: A total of 86 patients with a mean age of 64 years (range 2–92), presented with upper-limb ischaemia Sixty-two presented with acute ischaemia and 19 had chronic ischaemia and six resulted from trauma to the upper limb. The aetiology was cardiac/degenerative in 46 per cent, iatrogenic in 14 per cent, inflammatory in 8 per cent and thoracic outlet syndrome in 5 per cent The surgical procedures carried out were embolectomies in 45 patients, bypass reconstruction to the great vessels in 20 and distal upper limb reconstruction in 10. Five patients had thrombolysis of which three failed. There were four graft occlusions, two of whom required further surgery In the embolectomy group, there were four early and one late thrombosis, who required surgical intervention There were three limb losses, two patients had above-elbow amputation and one, hand amputation, and five re-occlusions for the embolectomies at 4-year follow up Two patients required above-elbow amputations and one required a hand amputation The limb salvage rate was 96.6 per cent and the 30-day mortality for the series was 7 per cent. Only one patient had ischaemic symptoms at follow-up

Conclusions: Upper limb ischaemia results from a multitude of underlying pathologies and therefore referral to a vascular specialist centre offering a full range of diagnostic and interventional procedures is recommended. We recommend surgical intervention in these patients to preserve limb function and prevent sequelae

Poster 047

Long-term results of surgical decompression of neurological thoracic outlet decompression

C.A. Maxwell-Armstrong,[1] B.S.W. Noorpuri[1], S. Abdul Haque,[1] D.M. Baker[2] and A.J. Lamerton[1]
[1]*Department of Surgery Lincoln County Hospital Greetwells Rd Lincoln and Department of Vascular Surgery, Royal Free Hospital, Pond Street, London NW3 6QG, UK*

Aims: Thoracic outlet compression syndrome is characterized by a variety of symptoms relating to compression of the neurovascular bundle. Relief of symptoms may be obtained following surgery in up to 99 per cent of cases.
Methods: The notes of patients operated on by a single surgeon using a supraclavicular approach were reviewed. Symptoms, pre-operative investigations, and complications were all documented. Outcome at 6 weeks, 6, 12 and 24 months follow-up was also recorded. In addition, all patients were contacted by telephone, in order to assess current level of symptoms.
Results: One hundred and thirty-eight patients underwent 146 operations (eight had bilateral procedures), over a 12-month period between October 1986 and March 1998. The case notes of 118 patients undergoing 126 operations were available for review. Symptoms were predominantly motor, sensory or vasomotor, and were present for a mean of 19.6 months prior to surgery. Complications were rare, but included pneumothorax requiring a chest drain ($n=1$) and infraclavicular anaesthesia ($n=13$). The mean duration of hospital stay was 2.1 days. At 6 weeks follow-up, 86.5 per cent of patients reported either an improvement, or complete resolution of their symptoms. Sixty-one patients were contactable, a mean of 55 months following decompression. Of these, 44 (72.1 per cent) were either improved or asymptomatic.
Conclusions: Decompression of thoracic outlet compression syndrome through a supraclavicular approach encompassing first rib resection leads to good long-term results with few complications.

Poster 048

Effect of pulsatile flow on the development of a tissue-engineered vascular graft

M.S. Baguneid, A. Seifalian, G. Hamilton and M.G. Walker
Department of Vascular Surgery, Manchester Royal Infirmary and Medical School, UK

Aims: To evaluate the effect of pre-conditioning smooth muscle cell rich hybrid grafts followed by conditioning a newly formed endothelium on both acute endothelial cell (EC) attachment and resistance to shear stress.
Methods: Non-endothelialized hybrid grafts of 1 week maturity were set up within pulsatile flow circuits for up to 14 days under strict physiological homeostasis. Metabolic activity and cellular distribution were evaluated using the Alamar blue$^{\text{TM}}$ assay and confocal microscopy. ECs labelled with 8 MBq of Indium 111 tropolonate were seeded onto both preconditioned and control non-preconditioned hybrid grafts. These were then conditioned using low flow rates for up to 72 h prior to assessing their resistance to shear stress. Measurements using a gamma counter were taken over 1 h and grafts were subsequently analysed by environmental scanning electron microscopy (ESEM).
Results: Pre-conditioning non-endothelialized hybrid grafts resulted in a significantly greater metabolic activity and increased proportion of contractile SMCs. This was reflected in a 40–50 per cent increased acute EC attachment ($P<0.05$) and greater resistance to shear stress at all time points ($P<0.05$). Furthermore, EC retention was significantly enhanced by a period of low flow conditioning. This was confirmed by ESEM, which demonstrated increased numbers of flattened ECs.
Discussion: Preconditioning non-endothelialized hybrid grafts and conditioning the newly formed endothelium significantly enhances both EC attachment and resistance to shear stress.

Poster 049

The role of subintimal angioplasty of calf vessels in lower limb ischaemia

H. Ingle, A. Nasim, M. Anderson, A. Bolia, G. Fishwick, R. Naylor, N. London, P.R.F. Bell and M. Thompson
Leicester Royal Infirmary, UK

Aims: To access the outcome of subintimal angioplasty in treating arterial disease below the adductor canal in patients with severe lower limb ischaemia.
Methods: A retrospective case note review was undertaken to look at consecutive patients undergoing subintimal angioplasty of calf vessels, for lower limb ischaemia between March 1997 and May 2000.
Results: Sixty-seven patients (70 limbs) were identified in the study period. There were 39 male patients (58 per cent) and 28 female patients (42 per cent), with a median age of 76 years (range 41–96). Risk factors included smoking (58 per cent), hypertension (54 per cent), diabetes (46 per cent), and IHD (27 per cent) Fifty-eight limbs (83 per cent) had critical limb ischaemia and 12(8 per cent) had severe claudication. In 25 (36 per cent) limbs a single vessel was recanalized, in 27 (39 per cent) two vessels were recanalized, in 15 (21 per cent) three vessels were recanalized and in one (1 per cent) all three vessels as well as poplitcal segment were recanalized. The mean length of occlusion was 24 cm (range 2–55). Angioplasty was technically successful in 64 (91 per cent) limbs. Complications included: self-limiting perforation in two (3 per cent), perforation requiring embolization in three (4 per cent) and distal embolus in one (1 per cent). The life table analysis is shown.

	Months				
	1	6	12	24	36
Survival percentage	97	92	81	57	50
Freedom from CLI percentage	90	83	83	83	83
Limb salvage percentage	95	94	94	94	94
No. of patients at risk	67	63	47	27	14

CLI, critical limb ischaemia.

Conclusions: Subintimal angioplasty is a safe and effective procedure for treating crural vessels in patients with severe limb ischaemia.

Poster 050

Relationship between handheld Doppler signals, infra-inguinal graft outcome and patient mortality

A.H.R. Stewart, A. Lucas, F.C.T. Smith, R.N. Baird and P.M. Lamont
Vascular Studies Unit, Bristol Royal Infirmary, UK

Aims: Handheld Doppler signals are recorded in the outpatient clinic in the majority of patients considered for infra-inguinal bypass grafts, as part of ankle–brachial pressure measurements and may give a better measure of run-off than arteriography. The aim of this study was to assess the relationship between handheld Doppler ankle signals, infra-inguinal graft outcome and patient mortality in a cohort of 258 consecutive infra-inguinal bypass grafts at one centre.
Methods: Ankle Doppler waveform characteristics were recorded in the outpatient department for patients considered for infra-inguinal bypass grafting. A score was assigned for Doppler signals from the anterior tibial, posterior tibial and dorsalis pedis arteries. Biphastic signals were scored 2, monophasic signals 1 and absent signals 0. A total Doppler score (0–6) was therefore calculated for each limb. Following bypass surgery, graft surveillance was undertaken using duplex ultrasound at 6, 12, 26 and 52 weeks. The relationship between Doppler run-off scores, graft patency and patient survival within the first year were analysed using Kaplan–Meier life table analysis and log rank tests.
Results: Between January 1995 and September 1999, 258 consecutive infrainguinal bypass grafts were performed on 242 patients. 210 patients (86.7 per cent) survived 1 years and overall primary assisted patency at one year was 79.3 per cent. A Doppler score of 0 was associated with a 1 year primary assisted patency of 50 per cent and a 1 year mortality of 50 per cent. As the Doppler score increased to 6 the graft patency increased to 100 per cent and the mortality decreased to 4.6 per cent

	Doppler score				
	0	1	2	3	4+
1-year graft patency (per cent)**	50.0	64.3	72.2	81.9	100
1-year morality (per cent)*	50.0	27.3	20.8	4.1	4.6

*$P=0.0002$ log rank test ;**$P=0.0015$ log rank test.

Conclusions: A run-off score based on handheld Doppler signals in patients undergoing infrainguinal bypass is significantly associated with both graft outcome and mortality over the first year. This may provide a means of stratifying risk in the outpatient clinic for patients considered for infrainguinal bypass grafts.

Posters 051

Stenting for localized arterial stenoses in the aorto-iliac segment

S Saha, M Gibson, E P H Torrie, T R Magee and R B Galland
Departments of Surgery and Radiology, Royal Berkshire Hospital, Reading, UK

Aims: To determine complications and patency following angioplasty (PTA) and stenting of aorto-iliac stenoses
Method: Between December 1994 and June 2000 54 patients (41 men), median age 64 years (41–89) underwent aorto-iliac stenting , A total of 63 stents were placed Indications were intermittent claudication in 42, rest pain in three and gangrene in nine. Sites stented were aorta nine, aorta and iliac three, common iliac 22, external iliac 14, common and external iliac two Bilateral iliac procedures were carried out in four. There were 11 recurrent stenoses The other reasons for stenting were residual stenoses greater than 30 per cent after PTA, tight calcified stenoses or when a stenosed iliac artery was being used as a donor prior to crossover or femoropopliteal bypass
Results: Technical success was achieved in 61 (97 per cent) cases The two failures were due to malposition as a result of proximal stent migration Two further patients sustained minor complications All 12 aortic stents were patent at a median follow up of 22 months (2–61 months). Of the iliac stents, two had occluded at a median follow-up of 15 months (0–69 months).
Conclusions: PTA and stenting of aorto-iliac stenoses can be safely achieved with durable results Control trials are needed to compare PTA with PTA and stenting

Poster 052

The role of primary stenting of iliac occlusions – early results

E P L Turton, P J Curley, P J Turner and C D. Irvine
Pinderfields District Hospital, Wakefield, UK

Aim To examine the role of primary stenting in iliac artery (IA) occlusion, in terms of technical success, and clinical results in a DGH.
Methods: Assessment was made of all IA stent placements performed using the Memotherm stent by a single vascular radiologist Data concerning 56 consecutive patients (median age 65 years, IQR, 58–73, 35 men, 62 per cent) was analysed. Indications included moderate claudication in 9 (16 per cent), severe claudication in 45 (80 per cent), and rest pain in 3 6 per cent There were 23 unilateral and 33 bilateral 'kissing' stents, for 26 with IA stenosis (46 per cent) and 30 with occlusion (54 per cent) The lesion length was >8 cm in 18 patients Patient outcome was determined on the basis of continued relief of symptoms and improvement to ABPI Median follow-up is 13 months (IQR, 7–26).
Results: Technical success was achieved in 98 per cent and no major complications occurred Patient reported walking distance and claudication symptoms improved in 55 patients, and the median ABPI improved from 0 53 (IQR 0 4–0.64) to 0 94 (IQR 0 8–1 0) Residual angiographically significant disease distal to the iliac arteries remained in 31 patients (55 per cent), of which 16 per cent was below knee, 45 per cent above knee, and 39 per cent at both sites Median increase in ABPI if residual disease present was 0 26, IQR 0 19–0 4 compared to 0 45, IQR 0 25–0 61 if not, $P=0\ 05$ Mann–Whitney U-test) However, this had no significant effect on walking distance There was no difference between those treated for occlusion or stenosis.
Conclusions: Iliac stenting effectively improves markers of distal perfusion and limb function even after chronic iliac occlusion Distal disease often coexists but has only a relatively small negative effect on overall benefit

Poster 053

The acquisition of methicillin resistant *Staphylococcus aureus* (MRSA) in vascular patients

J M Scriven, P Silva, R A Swann,[1] M M Thompson, A R Naylor, R F Bell and N J M London
Departments of Vascular Surgery, Robert Kilpatrick Building, University of Leicester, and [1]Microbiology, Leicester Royal Infirmary, UK

Aims: MRSA infection poses significant risks to patients undergoing arterial reconstructions The purpose of this ongoing study was to determine at what point during hospital admission MRSA was acquired
Methods: A consecutive series of patients undergoing vascular surgery during a six-month period were examined All patients underwent screening for MRSA using pooled moistened swabs taken from nose, throat, perineum and open wounds Swabs were taken at the following time points, on admission to the ward, exit from theatre, discharge from ITU, weekly on the ward whilst in-patients and on discharge from hospital.
Results: Seventy patients were admitted, of whom five (7 per cent) screened positive for MRSA on admission and a further 10 (14 per cent) became MRSA positive during their admission Of the 65 patients who were MRSA negative on admission all underwent surgery and 44 were admitted to the ITU. Of these 65 patients, the timing of the first MRSA positive swab was as follows exit from theatre 2/65 (3 per cent), discharge from ITU 3/44 (7 per cent) and on the ward postoperatively 5/65 (8 per cent). Of the 21 patients not admitted to the ITU, none became MRSA-positive at any time during their admission Comparing MRSA-negative ($n=60$) *versus* hospital acquired MRSA ($n=10$) patients (median, range), length of stay was 7 (3–60) *versus* 17 (9–61) days (Mann Whitney $P=0\ 000$), length of ITU stay 1 (0–21) *versus* 4 (0.5–21) days ($P=0\ 002$), patient age 67 (50–83) *versus* 73 (66–87) years ($P=0\ 025$)
Conclusions: These data suggest that 7 per cent of patients undergoing arterial surgery are pre-existing carriers of MRSA Although no particular factor appeared to result in MRSA acquisition, MRSA could be acquired throughout hospital admission and was commoner in those patients requiring a prolonged inpatient stay and admission to the ITU

Posters 054

Changes in vascular access surgical activity – an audit

D.C Mitchell, P A Lear, B D Pentlow, J D Morgan and G.C. Kerton
Dept of Surgery, Southmead Hospital, Bristol, UK

Aims: Audit of vascular access workload in a single renal unit
Methods: Audit of notes, renal unit database and operation register from 1 1 93 to 31 12.98.
Results: Some 1370 arterio-venous fistula (AVF, $n=1160$) and vascular access graft (VAG, $n=210$) operations were performed in 869 patients. Activity rose from 163 cases in 1993–299 cases in 1998 The total population on haemodialysis rose from 339 to 481 during this period The median age of AVF patients rose from 28 years in 1993 to 48 years by 1997, although the maximum age remained constant at about 88 years Patients undergoing VAG were older, with a median age of 52 years in 1993 rising to 57 years in 1998 Revisional surgery accounted for 18 7 per cent of AVF ($n=217$) and 25 7 per cent of VAG ($n=54$) During the period under study, the surgical complement of the renal failure service increased by a factor of 1 3 consultants while the workload increased by a factor of 1.8 These numbers take no account of the increasing complexity of providing vascular access in an ageing population. During the period under audit, four satellite dialysis units were opened in surrounding towns, two in 1995 and two in 1996 No local surgical provision was made for this expansion All but one of the towns has a vascular surgical service
Conclusions: The demand for vascular access surgery is rising rapidly in the U K This demand for surgery is not being matched by increased numbers of surgeons The diffusion of dialysis provision is not being matched by a corresponding diffusion of surgical provision, despite locally available skills Future expansion of consultant numbers needs to consider the needs of patients with renal failure

Poster 055

Bupivacaine application in the long saphenous vein tract following stripping is safe and provides prolonged analgesia

S M G Kibria, S Homer-Vanniasinkam, M J Gough and A I D Mavor
Department of Vascular Surgery, The General Infirmary at Leeds, UK

Aims: Early postoperative pain limits mobilization after varicose vein surgery, which is increasingly performed as a day-case procedure This study investigated the safety of a new method of administering local anaesthesia and the effect of this technique on postoperative pain
Methods: The study group comprised 20 consecutive patients undergoing unilateral long saphenous vein stripping for varicose veins. Bupivacaine 0 5 per cent, 10 mL, was introduced into the tract left after stripping the long saphenous vein by pulling a bupivacaine-soaked gauze into the tract for the remainder of the operation Blood samples were taken before placing the gauze, and at 0.5, 1, 2, 4, 6 and 8 h afterwards, and serum bupivacaine levels were assessed by gas liquid chromatography. Postoperatively the pain levels were assessed by a numerical rating scale and by the analgesic requirements during that period
Results: None of the patients showed any symptoms or signs of bupivacaine toxicity Peak serum levels occurred 1 h after introduction of bupivacaine (cumulative analysis) The maximum, recorded serum level (122 7 ng) was 200 times less than the known toxic level 18/20 patients considered pain relief excellent and none of the 18 required any postoperative analgesia during the first 24 h. A historical control group of 20 patients needed

between two and five (median three doses) doses of analgesia during the same postoperative period.

Conclusions: This method of delivering bupivacaine to the long saphenous vein tract after stripping is safe and provides excellent postoperative analgesia.

Poster 056

Varicose vein surgery using a tourniquet: a prospective randomized trial

A. Fowler and D.C. Mitchell

Department of Surgery, Southmead Hospital, Bristol, UK

Aims: A prospective randomized trial comparing the use of a tourniquet to no tourniquet in patients undergoing single-leg sapheno-femoral ligation, stripping and avulsions for varicose veins. The endpoints were blood loss, bruising and comparison of quality of life (QOL).

Methods: Forty-nine patients were recruited. Patients were operated on a single day-case list under the care of a single consultant. The Esmarch tourniquet was used in the tourniquet group. Blood loss was measured by weighing swabs and collection into a plastic drape protecting tray (Inflatec). Bruising was measured using a grid at 10 days. An SF36 quality of life questionnaire was administered pre-operatively, at 10 days and at 6 weeks post-operatively.

Results: Blood loss was significantly reduced by use of a tourniquet (mean 23 mL, range 4–110) compared with 91 mL (10–339) without tourniquet $P<0.001$. The amount of bruising (mean 74 cm^2, 14–200) with tourniquet was not significantly different to that (55 cm^2 10–150) without tourniquet ($P>0.5$). There was no difference in SF36 scores between the two groups, pre- or post-operatively.

Conclusions: Use of a tourniquet reduces operative blood loss, but does not reduce post-operative bruising or improve quality of life.

Poster 057

Superficial venous surgery for chronic leg ulceration in the presence of deep venous reflux

J. Barwell, C. Wakely, K. Harvey, J.J. Earnshaw, B.P. Heather, M. Whyman and K. Poskitt

Departments of Surgery, Cheltenham General and Gloucestershire Royal Hospitals, UK

Aims: To assess the anatomic and haemodynamic effects of superficial venous surgery on ulcerated legs with mixed deep and superficial venous reflux.

Methods: Seventeen legs with an ABPI >0.85, active or recently healed chronic ulceration and mixed deep and superficial venous reflux on colour duplex imaging underwent surgical correction of superficial reflux. Deep reflux was assessed in the following venous segments: common or superficial femoral, above-knee popliteal, below-knee popliteal. Colour duplex imaging was repeated following surgery. Digital plethysmography derived venous refill times (VRT) were calculated before surgery, with a narrow below-knee cuff, inflated to 80 mmHg to mimic the effect of surgery, and following surgery.

Results: Prior to surgery, seven legs had reflux in all deep venous segments and 10 had reflux confined to one or two deep venous segments (segmental reflux). The effects of surgery on the pattern of deep reflux and VRT are summarized in the table. Normal VRT is defined as >20 s.

	Deep reflux	Normal VRT	Normal VRT with BK-cuff
Legs with full deep venous system reflux ($n=7$)			
Before surgery	7**	7	1
After surgery		3	3
Legs with segmental deep venous system reflux ($n=10$)*			
Before surgery	10	1	6
After surgery	3**	4	

*$n=8$ for plethysmography data. **$P<0.01$ (χ^2).

Conclusions: Superficial venous surgery often corrects segmental deep venous reflux, but has no effect on reflux occurring throughout the deep system. Plethysmography-derived haemodynamic changes, which can be predicted preoperatively, did not mirror the colour duplex-derived anatomic changes.

Poster 058

Do variations in surgical practice influence neurological outcome in carotid endarterectomy?

J. Nagy, G.D. Griffiths and P.A. Stonebridge (On behalf of the Scottish Vascular Audit Group)

Department of Vascular Surgery, Ninewells Hospital and Medical School, Dundee, UK

Aims: To document variations in surgical practice during carotid endarterectomy (CEA) and to investigate whether these influence neurological outcome.

Methods: Prospective audit of surgical practice during CEA in Scotland between 1997 and 1999.

Results: Eight hundred and seventy-eight CEA were performed in 13 hospitals (mean 34 CEA per annum, range 4–82) by 34 consultant surgeons (mean 13 CEA per year, range 1–41). The neurological complication rate was 5 per cent. Surgeons performing less than 13 CEA per annum experienced a neurological complication rate of 8 per cent compared to 5 per cent for surgeons performing more (not significant). The mean percentage frequency for consultant practice is summarised: sinus nerve blockade (35.3 per cent, range 0–100 per cent); shunting (54.8 per cent, range 0–100 per cent); shortening (7.4 per cent, range 0–92 per cent); distal flap fixation (49.7 per cent, range 0–100 per cent); patching (73.3 per cent, range 0–100 per cent); dextran (19.3 per cent, range 0–100 per cent). Surgeons performing more than 13 CEA per annum secured distal flap in 52 per cent of cases compared to 42 per cent for surgeons performing less ($P<0.01$). Securing distal flap was associated with a neurological complication rate of 4.8 per cent compared to 8.5 per cent not secured ($P<0.05$). There were no other associations between surgical practice, numbers performed and neurological outcome.

Conclusions: Surgical practice varied widely between consultants. Securing the distal flap was the only manoeuvre that suggested fewer neurological complications.

Poster 059

Surgery for pulsatile tinnitus from occipital artery abnormalities

K.S. Zayyan, M.J. Forshaw and J.F. Colin

Norfolk and Norwich Hospital, Norwich, UK

Aims: A rare but potentially surgically curable cause of pulsatile tinnitus (PT) is occipital artery abnormality. We describe management and outcome of surgery in patients with the syndrome.

Methods: Ten patients with PT referred to a single vascular surgeon were carefully evaluated by history, physical examination and angiography to determine their suitability for occipital artery excision with curative intent. Surgical exposure and excision of the artery and its branches was performed through a curvilinear incision in the upper posterior triangle extending over the mastoid and temporal scalp, allowing complete removal of the vessel along with any abnormal vascular tissue.

Results: All 10 patients (six males, four females, mean age 68.2 years) had pulse synchronous tinnitus with audible mastoid bruits that disappeared on occlusion of the occipital artery but only six had abnormal communications of the occipital artery with the lateral sinus, although one of these six also involved communications with the vertebral artery. Three of the four patients who eventually had surgery were permanently cured while the fourth had mild recurrence after 5 years without symptoms and one had unexplained spontaneous resolution after angiography. One patient had extensive, inoperable AV malformation while the other four who were not operated on had extensive carotid abnormalities.

Conclusions: Selected cases of PT with angiographic evidence of occipital artery abnormalities may be cured by ligation and excision of the vessel. This relatively minor operation avoids the potential pitfalls of radiological embolization such as stroke and carotid dissection.

Training

Poster 060

An assessment of the skills base and attainments of SHOs on a regional BST programme

L. de Cossart, C. Wiltshire and J Brown
Countess of Chester Hospital, Mersey Deanery, UK

Aim: To assess the skills base and achievements of trainees on a BST training programme.

Methods: All trainees on a 3-year programme instituted in 1996 and designed to meet the requirements of the RCS England for MRCS were asked to complete a questionnaire designed to find out their aspirations and their opinions about the programme and its design The responses were anonymized to all involved in the analysis This paper reports the findings related to the trainees' logbook for the general surgical operations of abscess drainage, appendicectomy, inguinal hernia repair, upper and lower GI endoscopy, varicose vein surgery and small bowel anastomosis, all of which are listed in the blue book. The results were analysed by year of training and whether performed independently or supervised

Results: Eighty-four trainees returned analysable forms of which 50 per cent of trainees had entered the programme from PRHO posts

	Year 1	
	Independent	Seen
Abscess	17/38 (44.7%)	20/38 (52 6%)
Appendix	16/38 (42 1%)	18/38 (47 4%)
Hernia	6/38 (15 8%)	17 38 (44 7%)
VVs	6/38 (15 8%)	14/38 (36 8%)
Upper GI scopes	6/38 (15 8%)	11/38 (29%)
Flexi sigmoidoscopy	6/38 (15 8%)	10/38 (26 4%)
S-B anastomosis	3/38 (7 9%)	14/38 (36 8%)
	Year 2	
	Independent	Seen
Abscess	26/36 (72 2%)	29/36 (80 6%)
Appendix	22/36 (86 1%)	31/36 (61 1%)
Hernia	10/36 (27 8%)	31/36 (86 1%)
VVs	4/36 (11 1%)	22/36 (61 1%)
Upper GI scopes	4/36 (11 1%)	15/36 (41 7%)
Flexi sigmoidoscopy	7/36 (19 4%)	23/36 (63 9%)
S-B anastomosis	1/35 (2 9%)	25/36 (69 4%)
	Year 3	
	Independent	Seen
Abscess	7/8 (87 5%)	7/8 (87 5%)
Appendix	6/8 (75%)	7/8 (87 5%)
Hernia	3/8 (37 5%)	7/8 (87 5%)
VVs	5/8 (62 5%)	6/8 (75%)
Upper GI scopes	1/8 (12 5%)	7/8 (87 5%)
Flexi sigmoidoscopy	2/8 (25%)	8/8 (100%)
S-B anastomosis	1/8 (12 5%)	6/8 (75%)

Conclusions: Abscess drainage and appendicectomy are acquired by most trainees, usually as the 3 years progress but a few still do not achieve independence by year 3. The profession should insist on protected operative teaching (POT) for surgical trainees

Poster 061

To explore the views of basic surgical trainees on their training programme and their future in surgery

J. Brown, C. Wiltshire and L. de Cossart
Countess of Chester Hospital, Mersey Deanery, UK

Aim: To assess the views of basic surgical trainees on a recently instituted 3-year regional training programme in line with the requirements for the college exams. The particular areas of interest were the influences on their career choices, their aspirations for the future, and their satisfaction with the process of trainee including appraisal and assessment

Methods: A questionnaire designed in collaboration with the UK Medical Careers Research Group with structured questions and rated responses and an opportunity for free text expression was sent to 115 BSTs on the programme. Database construction and anonymous analysis was prepared by an educationist (JB). Presentation of results under the broad headings of BST background, career intentions, the regional scheme, assessment, exams and teachers. A specific analysis of the women is presented.

Results: Ninety-three trainees replied (81 per cent) 54 per cent (51) were graduates of the local university, 52.7 per cent (49) entered the scheme directly from PRHO posts, 4 3 per cent had more than 1-year's UK SHO experience, 28 per cent (26) were women. There was a definite parochial trend for choice of the programme. 71 per cent (66) of trainees made their career choice at university and about 25 per cent changed their surgical speciality choice, the strongest influences on these were teachers, SHO posts, and working conditions. Many trainees (43 per cent) were unsure of their progress; consultant feedback was the most desired.

Conclusions: This scheme was set up to satisfy college requirements and this review has demonstrated a young and inexperienced cohort of trainees who have strong convictions to pursue a surgical career They recognize the need for good appraisal from consultants and described CONSULTANT TRAiners as the most influential factor on their career choices

Posters 062

Electromagnetic motion analysis in the assessment of surgical technical skill

V K. Datta, S M Mackay, A A. Chang and A.W Darzi
Academic Surgical Unit, Imperial College School of Medicine, UK

Aims: Motion analysis has been validated as an objective measure of dexterity in laparoscopic surgical simulation. We aim to show the validity its application to skills assessment of open surgical tasks

Methods: Four subject groups were recruited: consultant general surgeons ($n=12$), senior specialist registrar (SSpR, $n=11$), junior specialist registrar (JSpR, $n=13$) and basic surgical trainee (BST, $n=12$). They performed a standardized laboratory-based small bowel anastomosis. Electromagnetic motion trackers placed on the backs of hands recorded positional data, and this was used to generate dexterity parameters, namely, number of movements made, time taken and distance travelled by hands (path length).

Results: Results, summarized in the table, are expressed as the geometric mean and 95 per cent confidence intervals. Kruskal–Wallis tests were performed to generate a mean ranking for each parameter

	No of movements	Mean rank movement
Consultant	1254 (875–1632)	11 9
SSpR	1375 (771–1978)	17 3
JSpR	1673 (1020–2325)	27 7
BST	2080 (1588–2573)	40 2

	Path length mm^{-1}	Time taken s^{-1}	Mean rank time
Consultant	18252 (9304–27200)	782 (527–1037)	12 7
SSpR	15700 (7560–23840)	842 (540–1144)	17 1
JSpR	17240 (8450–26030)	1016 (543–1488)	27.9
BST	14300 (9600–19000)	1236 (840–1632)	39 5

This was significant for both time ($P<001$) and movements ($P<0.01$). Mann–Whitney U tests between paired groups showed a significant difference for movements and time between BSTs and JSpR ($P<0\ 01$ movement and time), JSpR and SSpR ($P<0.05$ movement and time) There were no significance between SSpR and consultants for either parameter. Path length results were not statistically distinct between any of the groups.

Conclusions: Electromagnetic motion analysis is a valid objective measure of surgical dexterity in this laboratory-based model Bowel anastomotic performance appears to plateau at the higher specialist level

Posters 063

Registrar operating experience over a 15-year period: more, less or the same

G Morris-Stiff, E. Ball, D Harris, J Torkington and T. Havard
Department of Surgery, Royal Glamorgan Hospital, Ynysmaerdy

Aims: Concerns have been raised on the effects that Calmanization, the new deal on junior doctors hours, CEPOD recommendations, and increasing sub-specialization may have on the breadth and depth of operative exposure achieved during surgical training. This study looks at the changes in the operative caseload, both elective and emergency, over a 15-years period in one hospital

Methods: A retrospective review of theatre records was undertaken, looking at the caseload of the registrars working for two consultant surgeons at one

hospital in three one year periods spanning 15 years. The number, subspecialty, level of supervision and time of each operation was recorded.
Results: The total number of operations performed by each registrar is shown in the table.

	Registrar 1		Registrar 2	
Dates	Elective	Emergency	Elective	Emergency
1998–99	528	115	519	100
1991–92	506	90	522	103
1986–87	465	78	526	95

Although the crude total number of cases were similar over the 15-years period, differences emerged in subspecialty exposure, the types of emergencies and the percentage of emergencies operated after midnight.
Conclusions: Calmanization has not affected the number of cases operated upon by trainees. However, the case mix and the management of emergencies have been significantly affected.

General

Poster 064

Autologous transfusion: can you teach surgeons new tricks?

F. Torella, S.L. Haynes and C.N. McCollum
Academic Surgery Unit, South Manchester University Hospital, UK

Aims: The NHS Executive has recently recommended autologous transfusion (AT) to reduce homologous blood use. We investigated the changes in surgeons' attitude to AT over 10 years.
Methods: Questionnaires sent to surgeons practising in nine surgical specialities in 1990, 1994 and 1999.
Results: Response rates were 57 per cent of 265 in 1990, 56 per cent of 405 in 1994 and 57 per cent of 342 in 1999. Many surgeons were keen to use AT (85 per cent in 1990, 86 per cent in 1994 and 88 per cent in 1999). There was a small increase in the use of AT over 10 years (10 per cent in 1990, 13 per cent in 1994 and 24 per cent in 1999). In 1999, most surgeons knew of predonation (PAD) (95 per cent) and intraoperative cell salvage (ICS) (91 per cent), but only 75 per cent were aware of acute normovolaemic haemodilution (ANH) and 71 per cent of postoperative cell salvage (PCS). ANH and ICS were used more than and PAD and PCS. AT was used consistently only in general, orthopaedic and cardiothoracic surgery:
Results: The percentage of surgeons using autologous transfusion is shown in the table.

	PAD			ANH		
	1990	1994	1999	1990	1994	1999
General	8	8	0	10	9	13
Orthopaedic	0	5	31	0	3	22
Cardiothoracic	33	27	0	33	91	56
	ICS			PCS		
General	9	11	20	–	2	0
Orthopaedic	6	2	9	–	2	20
Cardiothoracic	33	91	100	–	73	67

Logistical obstacles, cost and staff related problems were consistently cited as reasons not to use AT.
Conclusions: Autologous transfusion was used sporadically in surgical practice. Clinical trials are needed to guide clinicians in the choice of transfusion techniques.

Poster 065

Prospective double blind randomized controlled trial of botulinum toxin A in axillary hyperhidrosis

M.T. Sinclair, W. Russell, N. Toosey, H. Manji, A.E.P. Cameron and I.S. Osman
Departments of Surgery and Neurology, Ipswich Hospital, Ipswich, UK

Aims: Does botulinum toxin A (BTA) reduce sweating in patients with axillary hyperhidrosis?
Methods: Ten patients with severe axillary hyperhidrosis were randomized to receive 200 mouse units of Dysport (BTA) injected subcutaneously into one axilla and placebo (P) into the other. Sweating was assessed quantitatively after a 30 min period of sweat provocation. Subjective sweating was measured using a 10-point linear analogue visual scale. Measurements were collected at baseline, 1 week, 4 weeks, 12 weeks and 24 weeks following injection. Mann–Whitney U-test was used for statistical analysis.
Results: All figures are median with interquartile range.

	P subjective score	BTA subjective score	P sweating (g)	BTA sweating (g)
Baseline	8.5 (6–10)	7.5 (4–10)	0.3 (0.1–1.5)	0.3 (0.1–1.2)
Week 1	8.5 (6–10)	5.5 (1.5–9.5)	0.6 (0.1–1.4)	0.2 (0.1–0.6)
Week 4	9.0 (6.5–10)	3.0 (1.5–5.5)*	0.6 (0.1–1.2)	0.2 (0–0.9)
Week 12	8.0 (5–10)	2.5 (1.5–4.5)**	0.6 (0.1–1.1)	0.2 (0.1–0.4)
Week 24	9.0 (6–10)	3.5 (1.5–6)***	0.4 (0.1–1.1)	0.15 (0–0.44)

There was a significant reduction in subjective sweating in axillas injected with BTA compared with placebo at 4 weeks (*$P<0.01$), 12 weeks (**$P<0.01$) and 24 weeks (***$P<0.02$) following injection. There was a trend towards a reduction in measured sweating in the BTA axillae.
Conclusions: Botulinum toxin A is effective in reducing sweating in axillary hyperhidrosis.

Poster 066

The effect of probiotics on bacterial translocation and septic morbidity in elective surgical patients

C.E. McNaught, N.P. Woodcock, C.J. Mitchell and J. MacFie
The Combined Gastroenterology Unit, Scarborough Hospital, North Yorkshire, UK

Aims: Bacterial translocation (BT) occurs in surgical patients and may account for postoperative sepsis. The aim of this study was to assess the effect of the probiotic *Lactobacillus plantarum* 299v (Proviva) on the incidence of BT and septic complications in elective surgical patients.
Methods: In this prospective trial, surgical patients awaiting major GI resection were randomized to receive an oral preparation containing *Lactobacillus plantarum* 299v for one week preoperatively and compared with a control group. All patients were taking a normal diet until the date of surgery. Bacterial translocation was assessed by the culture of mesenteric lymph nodes and serosal biopsies. Nasogastric aspirates were taken to establish gastric colonisation with enteric organisms. All septic morbidity was documented.
Results: 129 patients were entered into the study

	Proviva group ($n=64$)	Control group ($n=65$)	*P*
M:F ratio	39:25	36:29	
Median age (IQR)	68 years (58–74)	69 years (58–77)	
Bacterial translocation	7 patients (11.8%)	7 patients (11.8%)	>0.05
Gastric colonization	6 patients (11.0%)	8 patients (15%)	>0.05
Septic complications	7 patients (11.8%)	10 patients (15.3%)	>0.05

Conclusions: *Lactobacillus plantarum* 299v administration in elective surgical patients does not alter bacterial translocation rates or subsequent septic morbidity. The use of a preoperative probiotic had no effect on the incidence or nature of gastric colonization.

Poster 067

Changes in serum albumin concentration, other biochemical and haematological parameters, and bioelectrical impedance following crystalloid infusions in normal subjects

D.N. Lobo, Z. Stanga, J.A.D. Simpson, J.A. Anderson, B.J. Rowlands and S.P. Allison
University Hospital, Queen's Medical Centre, Nottingham, UK

Aims: The aims of this double blind crossover study were to determine whether 2 L bolus infusions of 0.9 per cent saline and 5 per cent dextrose produce hypoalbuminaemia in healthy subjects, and also to study the differential changes in serum and urinary biochemistry, haemoglobin and bioelectrical impedance analysis.
Methods: Ten male volunteers received 2 L infusions of 0.9 per cent saline and 5 per cent dextrose on separate occasions in random order over 1 h. Weight, haemoglobin, serum albumin, electrolytes and osmolality, and bioelectrical impedance were measured pre-infusion and hourly for 6 h. Subjects voided urine before the infusion and as necessary.

Results: The 10 male volunteers had a mean (SE) age of 22.1 (0.3) years, height of 1.78 (0.01) m, initial weight of 73.6 (1.8) kg and BMI of 23.2 (0.5) kg m^{-2}. Saline was the initial infusion in six subjects and dextrose in four. Subjects received the other infusion 7–10 days later. There was a mean fall in serum albumin concentration of 9 g L^{-1} (20 per cent) at the end of the saline infusion and of 7 g L^{-1} (16 per cent) after dextrose ($P<0.001$). This fall lasted more than 6 h after saline but returned to baseline 1 h after dextrose. Changes in haemoglobin and packed cell volume were less pronounced (7.5 per cent after saline and 6.5 per cent after dextrose). Weight increased by 2 kg with both infusions, returning rapidly to normal with the diuresis following dextrose, but remaining elevated for more than 6 h after saline infusion, as less than half the infused sodium and water had been excreted by this time. Transient hyponatraemia and hyperglycaemia followed by hypoglycaemia were noted after dextrose. Mean corpuscular volume did not change by more than ±1 fL from baseline during the 6 h after both infusions. Impedances rose after dextrose and fell after saline ($P<0.001$). Subjects voided more urine (mean 1663 *versus* 563 mL) of lower osmolality (mean 129 *versus* 630 mOsm kg^{-1}) after dextrose than after saline ($P<0.001$).

Conclusions: Even in normal subjects, saline infusions cause substantial falls in serum albumin concentration by dilution and redistribution, which last more than 6 h owing to the slow excretion of excess sodium. The value of bioelectrical impedance analysis to detect changes in body water is limited as results are dependent on the electrolyte content of the infused fluid.

Poster 068

Validity of government clinical indicator 'rates of death' within 30 days of surgery (emergency admission)

H. Teo, M. Simpson and R.C. Pearson

Manchester Royal Infirmary, UK

Aims: To assess the accuracy of the UK government's published 'Clinical Indicators' (CI), designed to monitor Trust performance and to allocate funding. The figures were widely used by Government and Press to create league tables of performance.

Methods: The case notes of all patients from our Trust who died within 30 days of emergency admission in February and March 1999, and who were included by Government in the CI database, were reviewed. Where appropriate, POSSUM data was validated and predicted mortality rates noted.

Results: There were 50 deaths included in the CI data. 47 notes were retrieved and reviewed. Of these 35 patients had been admitted with medical disease, 12 had undergone emergency surgery. The 35 medical admissions had been included on the basis of diagnostic, monitoring or resuscitative procedures such as endoscopy, urinary catheterization, central venous cannulation, external cardiac compression, each of which was included in the codes to be collected for official data. Of the 12 surgical cases, six were admitted under the care of surgeons using the POSSUM system. All bar one of these had a predicted mortality greater than 80 per cent.

Conclusions: The blanket collection of unqualified data, and its release for public scrutiny provides an inaccurate analysis of performance. Clinicians and Trusts should be wary of these methods and perform internal audit of data before submission to Government.

Poster 069

Stoppa repairs of complex or recurrent ventral giant hernias

A. Egun, I. Maddox, R.J. Corson, J. Hill, R.C. Pearson and I. MacLennan

Department of Colorectal and General Surgery, Manchester Royal Infirmary, Oxford Road, Manchester, UK

Aims: Incisional hernias occur in about 2–11 per cent of abdominal operations. They are difficult to repair, with recurrence as high as 30–50 per cent. We report our experience in the surgical management of these lesions.

Methods: Medical and audit records of 123 consecutive patients who underwent repair of giant ventral incisional hernia (greater than 10 cm in diameter) with the Stoppa technique (pre-peritoneal polypropylene mesh) were analysed. Demography, body mass index, number of previous repairs, co-morbidity, length of hospital stay and complications were recorded. Patient satisfaction following the operation was also assessed.

Results: Sixty-nine females and 54 males of mean age 57 (range 30–90) years underwent incisional hernia repair. The average BMI was 30.7 (range 18–50). 109 (89 per cent) of 123 patients had one or more contributory co-morbidity factors. 23 patients (18.7 per cent) had undergone two to four previous repairs. The median hospital stay was 6 days (range 3–77) and mean follow- up was 84 months (range 24–120). The complications were wound haematoma 5.7 per cent, chest infection 4 per cent, one pulmonary embolism and one reflux oesophagitis. Six patients (4.9 per cent) had wound infections. Five patients (4 per cent) had troublesome neuralgia. There was one death (0.8 per cent) and no recurrences despite one patient who had mesh removal because of deep wound infection. 92 per cent of the patients were satisfied with the outcome of their operation.

Conclusions: Prosthetic mesh repair for giant complex and recurrent hernias is safe, effective and well-tolerated by the majority of patients, many of whom have pre-existing co-morbidity.

Poster 070

Chronic pain after prosthetic mesh repair of groin hernia: laparoscopic *versus* open mesh repair

S. Kumar, S.J. Nixon, R.G. Wilson and I.M.C. MacIntyre

Dept of surgery, Alexander Donald Building, Western General Hospital, Edinburgh, UK

Aim: Chronic pain has been reported in 8–10 per cent of patients after groin hernia repair. This study aimed to compare the incidence of chronic pain after laparoscopic TEP or open mesh repair of groin hernia.

Methods: A questionnaire was sent to 441 patients, of whom 403 patients, mean age 64 years (range 20–94) responded. 208 had laparoscopic TEP repair and 195 open mesh repair between January 1998 and December 1999. The questionnaire was posted between 6 and 24 months after operation.

Results: Chronic pain was reported by 34/403 (8 per cent) of patients. 9/208 (4.3 per cent) of patients reported groin pain after laparoscopic repair compared to 24/195 (12.3 per cent) after open mesh repair ($P<0.01$). Both groups of patients were comparable in age and sex distribution.

Conclusion: We conclude that chronic pain reported by 8 per cent of the patients was significantly more common after the open than laparoscopic mesh repair.

Poster 071

Appendicitis is unlikely in children with acute abdominal pain who have caecal gurgling

G. McGreal, J. Kelly, J. O'Donnell, W. Kirwan, M. Brady and H.P. Redmond

Academic Department of Surgery, Cork University Hospital, Wilton, Cork, Ireland

Aims: While many clinical signs are described to diagnose appendicitis, less emphasis has been placed on signs that may exclude this diagnosis. We analysed a clinical sign, called 'caecal gurgling', that may help identify children with abdominal pain in whom appendicectomy may be avoided.

Methods: One hundred and one children admitted with a presumptive diagnosis of appendicitis were prospectively and independently examined for right iliac fossa (RIF) tenderness, guarding and caecal gurgling (CG) by two examiners not otherwise involved in their care. CG is elicited by palpation in the right iliac fossa, being positive if a gurgling sensation is felt, like when reducing a hernia-containing bowel. Signs were correlated with the ultimate diagnosis (resolution of pain without surgery, appendicectomy, histology of appendix). Overall accuracy, sensitivity, specificity, positive and negative predictive values and the kappa statistic for inter-observer variability were calculated. Comparison of groups was by Fisher's exact test.

Results: The majority of children with CG settled spontaneously.

	Gurgling ($n=47$)	No gurgling ($n=48$)	P
RIF tenderness	38	45	NS
Guarding	15	23	NS
Appendicectomy	7	25	<0.005
Acute appendicitis	2	21	0.01

Caecal gurgling had a specificity of 91 per cent and a positive predictive value of 85 per cent in identifying patients who resolve without appendicectomy. The kappa value was 0.88.

Conclusions: Caecal gurgling has now been critically analysed for the first time, demonstrating excellent specificity and inter-observer variability. It may help to reduce negative appendicectomy rates in children.

Index to Authors

Abdul Haque, S. 76
Abidia, A 12
Abidia, A F. 17
Abraham, A.T. 12
Abu-Omar, Y. 75
Acher, P 51
Achuthan, R. 65
Adam, D.J. 44
Adams, M. 70
Ahmad, N. 19, 37, 48, 60, 68
Ahmed, I 19, 37
Akhavani, M.A. 52
Akyol, M. 37
Al-Ali, J. 74
Al-Bader, M. 74
Ali, B. 34
Allan, A 69
Allen, E. 66
Allen-Mersh, T.G 56
Allison, S.P 25, 46, 80
Al-Mishlab, T. 51
Almond, J. 31
Al-Mufti, R A 14
Ambrose, N S. 57
Amin, A 68
Ammori, B J 13
Anand, P. 10
Anderson, J.A 80
Anderson, J H 52
Anderson, M. 76
Anderson, N G 6, 33
Anderton, M. 49
Armstrong, M.A. 6
Arnold, D. 66
Artioukh, D.Y. 69
Arulampalam, T H A 56
Arun, C 56
Asfar, S K 74
Asher Dean, R. 7
Ashley, S 63
Ashley, S W 15
Atkinson, H D. 59
Attia, M 60, 48, 68
Attia, M S 19, 37
Attwood, S.E.A. 15, 54
Austen, W G 19
Austin, K.K. 7
Awere, L M. 34
Ayub, K 14

Bachoo, P. 75
Baguneid, M.S. 76
Bahia, H. 12
Baird, R N. 17, 50, 76
Baker, A R 50
Baker, D.M. 4, 5, 76
Baker, R.P 56, 73
Balaji, N.S 63
Balan, K K 33
Ball, E. 79
Bannister, J 23
Barclay, G. 13
Barker, P 39, 39
Barker, P A. 38
Barratt, N 17, 17
Barrett, D 72
Barros D'Sa, A.A B 5, 74
Bartram, C I 26
Barwell, J 78
Bassi, C. 31
Bates, T 40, 41, 51
Baum, M. 41
Baxter, J.N. 30
Beardsmore, D M. 66
Becker, M. 67
Beger, H.G 31
Bell, J 40
Bell, J A 6
Bell, N 27
Bell, P R. 49
Bell, P R.F. 76
Bell, R.F. 77
Bellamy, C O. 2
Belt, E. 27
Bendall, S. 40
Bennett, D H 35
Bennett, M.K. 25
Berridge, D C. 50, 62, 62
Berry, D.P 6, 8
Bevan, L 72
Beynon, J 52, 72
Bhasker, S. 50
Bhowmick, A. 16
Bickmore, W 2
Bicknell, C D 44
Bicknell, G.R 10, 26, 36
Biffin, A. 31
Bird, R L 62
Birks, M. 42
Blamey, R W. 6, 40, 66
Boermeester, M.A 27
Boffard, K.D 39, 39
Boland, G P 41
Bolia, A. 76
Bonnici, C. 16
Bostock, K A. 25
Bouchier-Hayes, D. 4
Bouchier-Hayes, D.I 20
Bouchier-Hayes, D J. 13, 20, 21
Boulos, P.B 10, 56
Bowley, D M G. 35, 39, 39
Bowyer, R.C 67
Boyle, S 2
Bradbury, A W. 44
Brady, M. 81
Braithwaite, B 74
Brown, G 25
Brown, J 79, 79
Brown, L C. 17, 17
Brown, T H. 30
Brown, T J 46
Browse, D 69
Bryce, J 17
Buchler, M W. 31
Buckels, J.A C 48
Bundred, N 66
Bundred, N J 6, 33, 41
Burden, P. 64
Burke, C. 70
Burnley, S 16
Burnnd, K.G. 1
Burns, J 59
Butler, C M 28
Bygrave, S. 60
Byrne, D.S. 63
Byrne, J P 54

Cade, D 51
Cahill, R.A 12
Callery, M.P 13
Cameron, A E P. 80
Campbell, F.C. 5, 6
Campbell, L 32
Campbell, W.B 23
Candinas, D 48
Carlson, G.L 2
Carmichael, A.R. 28
Carr, M. 12
Carr, N.D. 52, 72
Carter, C.R 58
Cartmell, M T. 67
Casey, J.F 54
Cassar, K. 49
Chalmers, R.T.A 45
Chan, C L.H. 10, 52
Chan, K C 41
Chan, S Y. 66
Chang, A 46
Chang, A.A. 46, 79
Chapman, M A.S. . 69
Chari, R S. 13
Charles, J. 31
Cheah, L P. 22
Cheetham, M.J 72
Cheshire, N 46
Cheshire, N J.W. 44
Chetter, I. 12
Chetter, I C. 17, 62, 62
Chetty, U 40
Cheung, K.L. 66
Chisholm, E.M 47
Chong, P 58
Chong, P.F S. 3, 17, 17
Church, R D 73
Claridge, M 73
Clark, E.C 2
Clark, G.W.B 54, 66
Cleary, P E 11
Cohen, C.R G. 72
Coker, J 16
Coleridge Smith P.D. 4
Colin, J F 78
Collin, J 62, 64
Collins, C. 42
Collins, H M. 7
Collins, M. 1
Conaghan, P J 22
Condron, C 4, 20
Cooke, T.G 40
Cooper, G. 75
Cooper, M J 23
Corps, C L. 37
Corson, R J 81
Cosgrove, C. 63
Costa, D.C 56
Costello, P. 7
Cottorrell, G 17, 18
Coull, D B 52
Coulthard, R A. 59
Cowan, A R 44
Cowey, A. 39
Crellin, A 66
Crinnion, J N. 74
Crombie, N 40
Cross, K.S. 75
Crotty, T. 3, 65
Crumplin, M K.H. 31
Cullen, N. 70
Cummins, K. 60
Cunningham, D C 25
Curley, P J 77
Currie, E 60

Dall, B. 65
Daniels, I 47
Darakhshan, A A 69
Darzi, A. 46, 46, 56
Darzi, A W 46, 79
Dashwood, M.R *1*, 4, 5
Datta, V. 46
Datta, V.K. 46, 79
Davidson, B R. 1, 12
Davidson, T. 32
Davies, A.H. 3, 17, 17
Davies, A.R 58
Davies, R J. 42
Dawson, P.M 70
Dawson, R. 58
Day, A 17
Day, N.E. 74
de Beaux, A C. 66
de Cossart, L 17, 18, 44, 79, 79
De Jong, K. 59
De Ville De Goyet, J 48
Delaney, C P. 42
Delaney, P 38
Demaine, A G. 14
Dennison, A R. 6
Denton, L. 44
Dervernis, C. 31
Devitt, P.G 54
Dexter, S.P L 53, 53
Dey, P. 66, 51
Dimitri, S 17, 18, 44
Dixon, J.M 40
Dodds, S. 69
Dolan, K. 53, 53
Douek, M 67
Dowidar, N. 58
Doyle, M 9, 10
Dresner, S M. 25, 53, 55
Drumm, J. 38
Dube, M.G 46
Duffy, M.J. 65
Dugdill, S. 49, 75
Duncan, J L. 49
Dundas, S R. 2
Dunn, J.A 31
Durdey, P. 42
Duthie, G S. 56, 73
Dutta, S 32
Dyer, N.H C. 10
Dzik-Jurasz, A S.K 25

Earnshaw, J.J 63, 63, 78
Eatock, F.C. 58
Eccles, S A. 25
Edwards, A. 75
Edwards, P.R. 17, 18, 44
Egger, M 43
Egun, A. 81
Ell, P.J 32, 56
Ellis, I O. 6, 40
Ellis, M 17, 17
Ellison, D 16
Encke, A 47
Engeset, J. 75
Erwin, P 1
Evans, C. 36

Facer, P 10
Fanning, N P. 28
Farouk, R 42
Fassiadis, N. 49
Favuzza, J. 19
Fazio, V W. 42
Fearn, S J 25
Fennessy, M 41

Fernandez-Cruz, L. 31
Fernando, K.J. 34
Fieldman, N.R. 67
Figueira, E. 22
Filbey, D. 4
Fink, M. . 48
Finlay, I.G. 52
Fischer, C.P. 59
Fishwick, G. 76
Fitzgerald, P. 13
Flett, M.M. 40, 63
Flood, H. 38
Forbes, J.F. 58
Forrest, A.P.M. 40
Forshaw, M.J. 74, 78
Forsythe, J.L.R. 32, 37
Fossard, D.P. 22
Foster, M.E. 31, 58
Fountoulakis, A. 53, 53, 54
Fowler, A. 78
Foy, C. 63
France, M. 27
Franklin, I.J. 70
Fraser, I.A. 35
Friend, P.J. 36, 73
Friess, H. 31
Fuchs, D. 56
Fuggle, S. 36
Furness, P.D. 6

Gafar, H.A. 74
Gall, R.B. 77
Galland, R.B. 63, 64
Gallegos, N. 71
Galloway, D. 69
Game, P.A. 54, 24
Gang, C. 20
Garden, O.J. 2, 32, 37, 58, 59, 59, 60
Gardiner, K.R. 1
Garlick, N.I. 5
Garratt, A.M. 3
Garrodd, D. 15
Gawish, A. 74
George, M.L. 25
Ghaneh, P. 7
Ghosh, D. 70
Ghosh, D.B. 35
Gibbons, C.P. 30
Gibson, M. 77
Gillams, A. 68
Gilliam, A.D. 1
Godbole, P. 38
Goddard, J.C. 6, 8
Godden, D.J. 49
Going, J. 40
Golledge, J. 3, 17, 17
Goode, A.W. 32
Gooding, J. 23
Goosen, J. 39, 39
Gosling, P. 16
Gough, M.J. 44, 77
Gould, T. 42
Gouma, D.J. 27
Grace, K.L.R. 42
Grace, P.A. 38
Graham, A.N.J. 6
Gray, D.W.R. 48
Green, C. 70
Green, J. 68
Greenhalgh, R.M. 3, 17, 17
Gregory, J. 39
Griffin, S.M. 25, 30, 53, 55
Griffiths, G.D. 23, 78
Grimble, S.A.J. 64
Guillou, P.J. 54, 57, 66
Gunson, B.K. 48
Guthrie, A. 57

Haas, S. 47
Haggart, P.C. 44
Halliday, M.I. 5
Halligan, S. 26
Halloran, C.M. 7
Halverson, A. 42
Hamer-Hodges, D.W. 27
Hamilton, G. 16, 63, 76
Hammond, L.J. 32
Handa, A. 62, 64
Hands, L. 62
Hands, L.J. 64
Hannon, R.J. 2
Haq, A.I. 70
Hardie, L.J. 54
Harkin, D.W. 5
Harris, A.M. 30
Harris, C.A. 23
Harris, D. 79
Harrison, E. 68
Harrison, R. 15
Harrison, T.A. 42
Hart, R.S. 58, 67
Harvey, K. 78
Hasegawa, H. 71
Havard, T. 79
Hawkins, W. 2
Hayes, N. 25, 30, 53, 55
Haynes, S.L. 20, 80
Healy, C. 28
Heather, B.P. 63, 78
Hechtman, H.B. 19
Heitmann, M. 67
Hemingway, D.M. 56
Henderson, D.C. 56
Heriot, A.G. 51
Heriot, G. 67
Hersman, G. 39
Heys, S.D. 7
Hick, D.G. 54
Hicks, E. 58
Higgins, G.T. 11
Hill, A.D.K. 28, 65
Hill, J. 81, 27
Hill, M.E. 25
Hill-Wilson, G. 25
Hindmarsh, P. 66
Hine, C. 50
Hodder, R. 51
Hoile, R.W. 28
Holbrook, R. 70
Holdstock, J.M. 49
Holtham, S.J. 49, 75
Homer-Vanniasinkam, S. 44, 77
Horgan, K. 65
Horsburgh, T. 73
Hosie, K.B. 52
Houghton, J. 34, 41
Howlader, M.H. 4
Huang, A. 56
Hubbard, C.S.F.F. 74
Hughes, D. 73
Humphreys, W.V. 28
Hunt, L. 30
Husband, J. 25
Hutchins, R.R. 58
Hutchinson, R. 73
Hutchinson, S. 25

Ibrahim, K. 1
Imber, C.J. 36, 73
Imrie, C.W. 58
Ingham Clark, C.L. 22
Ingle, H. 76
Irvin, T.T. 70
Irvine, C.D. 77
Ismail, M.A. 73

Jack, W. 40
Jamieson, G.G. 54, 66
Jankowski, J. 70
Jankowski, J.A. 15
Javed, M.S. 68
Jenkins, A.McL. 45
Jewkes, A. 28, 28
John, T.G. 60
Johnson, B. 17
Johnston, D. 53
Johnston, P. 28, 28
Jonas, M. 51, 71, 72
Jones, J.L. 8
Jones, P.A. 32
Joyce, M. 13
Judge, C. 63
Junnarkar, S. 2
Jurewicz, W.A. 36
Jutley, R.S. 38

Kage, A. 67
Kaihara, S. 15
Kairsingh, S. 16
Kakkar, A.K. 13, 47
Kamm, M.A. 26, 72
Kapila, L. 38
Karanjia, N. 67
Karanjia, N.D. 51
Karat, D. 53, 55
Kardirkamanathan, S. 71
Kavanagh, E. 12
Kay, E. 20
Kearns, S.R. 4, 21
Keaveny, T.V. 3, 65
Keenan, R.A. 69
Keighley, M.R.B. 51, 71, 71
Kell, M.R. 14
Kelly, C. 4, 21
Kelly, C.J. 13, 20, 20
Kelly, J. 81
Kennedy, R. 42
Kent, P.J. 50, 62, 62
Kerle, M. 63
Kerle, M.I. 44
Kerr, D.J. 31
Kerton, G.C. 77
Kerwat, R. 31
Kesecioglu, J. 27
Keshtgar, M. 32
Kessaris, N. 42
Kessel, D. 44, 50
Kester, R.C. 50, 62, 62
Kianifard, B. 49
Kibria, S.M.G. 77
Kim, B.S. 15
Kim, R.D. 13
Kimber, M.R. 36
Kimber, R.M. 19
Kingsnorth, A.N. 14, 35, 67
Kirwan, W. 81
Kirwan, W.O. 7
Kitajima, M. 71
Kmiot, W.A. 26
Knowles, C.H. 10
Knox, F. 6
Knox, W.F. 33, 41
Kobzik, L. 19
Kocher, H.M. 42
Kocjan, G. 32
Kockelbergh, R.C. 8
Korsgen, S. 69
Koti, R.S. 1
Krijgsman, B. 16
Krukowski, Z.H. 69
Kuhan, G. 12, 17
Kumar, A. 7
Kumar, S. 81
Kurian, K.M. 32
Kyaw, M. 67
Kyriakides, C. 19

Lacaine, F. 31
Lamb, P.J. 53, 55
Lambah, P.A. 40
Lambert, A.W. 52
Lamerton, A.J. 76
Lamont, P.M. 17, 50, 76
Larvin, M. 1, 13
Latteier, J. 41
Lau, L.L. 2
Lawes, D. 39
Leach, M.O. 25
Leahy, A. 13
Leaper, D.J. 34
Lear, P.A. 50, 77
Leather, A.J.M. 42
Ledermann, J. 68
Lee, A. 32
Lee, B. 2
Lee, D.M. 32
Lee, E.J.K. 23
Lee, P.W.R. 56
Lees, T.A. 49, 75
Lees, W. 68
Lewis, A. 5
Libertiny, G. 48
Lindsey, B. 63
Linforth, R.A. 6, 33
Link, K.H. 31
Lo, S. 27
Lobo, D.N. 25, 46, 80
Lodge, J.P.A. 19, 37, 48, 60, 68
Loftus, I.M. 22
Loisidou, M. 56
London, N. 49, 76
London, N.J.M. 56, 77
Lopez, I. 36, 73
Lord, R.H. 36
Lotzof, K. 62
Loveday, E. 50
Lovett, B. 34
Lowe, J. 62
Lubbers, M.J. 27
Lucas, A. 76
Ludlam, C.A. 44
Lund, J.N. 38
Lunniss, P.J. 52, 69
Luscombe, J. 75

MacDonald, L. 52
MacFie, J. 30, 68, 80

Macintyre, I.M.C. 81
Mackay, S. 46
Mackay, S M 46, 79
MacKenzie, S. 69, 69
Mackey, P 52, 72
MacLean, M E. 40
MacLennan, I. 39, 81
Macmillan, D M 6, 40
MacRae, K 41
MacSweeney, S T 62
Maddox, I. 81
Madhavan, K.K. 37, 58, 59, 59, 60
Magee, T R. 63, 64, 77
Mahmood, A 75
Mahon, C C.W 10
Majumder, B. 7
Mandalia, M 46
Mandalia, M R 46
Manji, H. 80
Mann, C 19
Manning, B 9
Manning, B.J 9, 9
Mansfield, A O 44
Marcus, A.J. 62
Marriott, S 70
Marsh Jr, H 19
Marshall, J. 73
Marson, L P 32
Martin, I.G 13, 53, 54
Martin, V 62
Masoud, A 30
Mathie, R.T 14, 14
Mavor, A I D. 44, 77
Maxwell, P 6
Maxwell-Armstrong, C A 76
Mayer, D.A 48
McAllister, I. 6
McCaigue, M. 1
McCallion, K. 5
McCarthy, P 3, 65
McCollum, C.N 16, 19, 20, 25, 80
McCollum, P T 12, 17
McCormack, D 39
McCune, K H. 1
McDermott, E.W. 28, 65
McGreal, G 12, 81
McGuigan, J.A. . 6
Mcguire, J. 73
McIntosh, S.A. 33
McKay, A J 63
McKay, C J 58
McKee, R.F 52
McLaren, K. 32
McLaughlin, R 20
McMahon, M J. 1, 13, 53
McManus, K.G 6
McMaster, P. 48
McNab, C. 39
McNaught, C.E. 30, 80
McPherson, S. 44
McWilliams, D 1
Mehigan, D 3, 65
Melling, A.G. 34
Menezes, N 58
Menon, K. 48, 60, 68
Menon, V S. 30
Mercer, S.J. 52
Metcalfe, M.S. 10, 19, 26, 36,
  36, 73
Miller, C 35
Millns, P. 16
Mirakian, R. 32
Mirza, D F. 48
Mirza, M. 69
Mitchel, G 17, 44
Mitchell, A. 17, 17
Mitchell, C.J. 30, 68, 80
Mitchell, D.C. 77, 78
Mitchell, D.M 50
Mitchell, P 39
Mittal, T. 36
Modhwadia, D. 26
Moffit, D.D. 31
Mofidi, R 3, 65
Moir, S. 7
Molloy, R.G. 69
Molostvov, G. 5
Moneley, D 20, 4, 20, 21
Monson, J R.T. 56
Moody, A.R 62
Mooney, D.L 15
Moore, F.D. 19
Moore, K. 13
Moreea, S 68
Morgan, J D 77
Morgan, P. 46
Morris, A. 5
Morris, A.G 70
Morris, C D. 15, 54
Morris, P J. 48
Morris-Stiff, G. 79, 36
Morse, M. 50
Morton, D. 70
Morton, D.G. 51, 71
Moseley, L. 58
Moses, A.G W. 58
Mosquera, D. 5
Motson, R.W 71
Mulholland, K 6
Munot, K 65
Munro, E.N 50
Murie, J A. 45
Murphy, G J 10, 19, 26, 36, 36, 73
Murphy, K.P 50
Murphy, R.E. 62
Murphy, T. 14
Murray, P 4, 21
Myers, J C 54
Mylonakis, E 51, 71, 71

Nagy, J. 23, 78
Nash, G F 13
Nash, R. 74
Nasim, A 76
Navaratnam, R.M. 53
Naylor, A.R 77
Naylor, R. 49, 76
Neal, K R. 25, 46, 72
Neary, B. 63
Neary, P. 56, 73
Neoptolemos, J P. 7, 31
Newbold, M. 70
Nicholls, R J. 26
Nicholls, T. 26
Nicholson, M.L 10, 19, 26, 36,
  36, 73
Nicolaides, A N 16
Nixon, S J 81
Noorpuri, B.S.W. 76
Norton, I 39
Noujaim, H M. 48

O'Bichere, A. 70
O'Boyle, C. 66, 54, 24
O'Brien, D. 20
O'Byrne, K J. 6, 8
O'Connell, P R 42
O'Donnell, J. 81
O'Donoghue, D.P. 28
O'Donovan, A 38
O'Dwyer, P J. 69, 69, 43
O'Higgins, N 65, 28
O'Reilly, A D 14, 67
O'Riordain, D S. 54, 57
Obertop, H 27
Obholzer, R.J. 67
Ogunbivi, O 70
Ogunbiyi, O.A. 69
Oniscu, G.C 37
Osman, I.S. 80
Ostick, D.G 23

Pacifico, M 58
Padhani, A.R. 25
Pai, M. 64
Palazzo, F.F 32
Palmer, J. 72
Papavassiliou, V. 49
Parks, R W 58, 59, 59, 60
Parry, D. 44
Patel, B 34
Patel, J. 44, 50
Paterson, I. 67
Pearson, E. 69
Pearson, R.C. 27, 39, 81, 81
Peck, D 56
Pederzoli, P 31
Pentlow, B D. 77
Perkins, A C 25
Phillips, D 62, 64
Phillips, R.K 70
Phillips, R.K.S 72
Pierro, A 20
Piggott, D 36, 73
Pillarisetti, R.R 31
Pillay, W R 74
Pinder, S E. 6, 40
Pleass, H. 37
Pollard, S G 48
Pope, I 27
Porter, C. 35
Porter, K.E 56
Poskitt, K. 78
Potter, M W 13
Potts, D.J. 19, 37
Powell, J.T 3
Power, C 12, 9
Prance, S. 32
Prasad, K.R 48, 60, 68
Prescott, R J 40
Punson, G 16
Purushotham, A.D 33
Pye, J K. 31

Quick, C.R.G. 74
Quin, R O 63

Radford, M. 28, 28
Radley, S 51, 71
Radtke, A. 60
Rahman, S H. 1, 13
Raines, S.A 55
Ralphs, D. 32
Rampaul, R.S. 6, 40
Ravindra, K V 48, 60, 68
Raza, Z. 45
Redmond, H.P. 12, 12, 7, 9, 9, 9,
  9, 10, 11, 81
Redmond, K.C. 7
Rees, M. 60
Rees, M R. 50
Remzi, F H. 42
Renehan, A.G. 43
Renwick, P. 17
Reynolds, J.V. 14
Ridgway, P 56
Ridgway, P F. 65
Riding, G 25
Riley, D.L. 41
Rittoo, D. 16
Roberts, A 17, 18
Roberts, J.R 14
Robertson, I. 44, 50
Robertson, J F.R. 6, 40, 66
Rodd, C D 62
Rogers, P N 63
Rohlke, W 19
Rose, J 49, 75
Rose, K. 67
Rosin, R.D 34
Ross, J.A. 2
Rowland, I J 25
Rowlands, B.J. 25, 46, 80
Rowlands, T. 44
Royle, C. 42
Russell, W 80

Sabetai, M.M 16
Saeb-Parsey, K 52
Safar, H. 74
Safranek, P. 27
Saha, S. 77
Saini, A 62
Salacinski, H.J 16
Salaman, R 75
Sanders, G 52
Sarela, A.I. 54, 57
Sargen, K 67
Saunders, M.P. 43
Saunders, R N 10, 19, 26, 36,
  36, 73
Savage, F J 10
Saville, S 36
Sawyer, W 34
Scholefield, J.H. 7, 38, 51, 71, 72
Schrimph, D 28
Scot, D J A. 44, 50, 62, 62
Scott, E.M 34
Scott, S.M. 52
Scriven, J.M. 77
Scully, M.F. 13
Seal, C 30
Seifalian, A. 76
Seifalian, A M 1, 16
Selvachandran, S N 51
Senagore, A.J. 42
Seymour, M.T. 57
Shah, S A 13
Shah, S.R. 12
Shaw, M 74
Sheehan, J.J. 28
Sheehan, S. 65
Sheehan, S.J. 3
Shenfine, J 53
Sheppard, M 16
Sheridan, M. 66
Shiralkar, S 28
Shrestha, P.C. 60

Silva, P. 77
Simms, M.H. 16, 75
Simpson, J. 38, 51
Simpson, J.A.D. 80
Simpson, M. 81
Sinclair, M.T. 80
Singh, I. 1
Sinha, P. 40
Sintler, M. 75
Sirivatanauksorn, Y. 12
Siriwardena, A.K. 34
Slater, N. 42
Sloan, J.M. 6
Smith, A. 1
Smith, F.C.T. 17, 50, 76
Smith, G.C.S. 59
Smith, H.C. 63
Smith, J.A.E. 27
Smith, J.J. 70
Smith, S.G.T. 46
Smith, S.R.G. 16, 75
Smye, M.G. 2
Sookhai, S. 12, 7, 9
Soong, C.V. 2
Souza, D.S.R. 4
Spark, J.I. 62, 62
Speake, W. 51
Speake, W.J. 7
Spence, G.M. 6
Spencer, J. 57
Spooner, D. 31
Springall, R.G. 70
St. Peter, S.D. 36, 73
Stanga, Z. 80
Stansby, G. 16
Stephen, A.E. 15
Stewart, A.H.R. 76
Stewart, G.D. 60
Stinchcombe, C. 27
Stonebridge, P.A. 23, 78
Stones, C. 69
Street, J. 9
Stringer, M.D. 38
Stuart, W. 45
Sue-Ling, H.M. 53, 53, 54, 66
Super, P. 67
Sutton, C.D. 6, 8
Swann, R.A. 77
Sweeney, K.J. 14
Swift, R.I. 25
Sykes, K. 17, 18
Sykes, T.C.F. 5
Synott, K. 39

Tait, D. 25
Tambiah, J.R.S. 3
Tan, S.M. 66
Tate, J.J.T. 59
Tavakkolizadeh, A. 15
Taylor, I. 32, 34, 56, 68
Teasdale, C. 32
Tegos, T.J. 16
Tekkis, P.P. 42
Tennant, W. 62
Teo, H. 81
Thethy, S. 37
Thomas, B.J. 16
Thomas, M.G. 42
Thompson, C. 13, 20
Thompson, M. 76
Thompson, M.H. 59
Thompson, M.M. 49, 77
Thompson, R.J. 38
Thomson, A.M. 23
Thornton, M.J. 50
Thrush, S. 40
Tillin, T. 52
Toogood, G.J. 48, 60, 68
Toosey, N. 80
Torella, F. 20, 80
Torkington, J. 46, 79
Torrie, E.P.H. 77
Tranter, S.E. 59
Tsavellas, G. 56
Tselepis, C. 15
Tsui, J.C.S. 4, 5
Turner, M. 69
Turner, P.J. 77
Turton, E.P.L. 77
Tytherleight, M. 42
Umughete, A. 70
Underwood, D. 2
Upponi, S.S. 33

Vacanti, J.P. 15
Van de Sijpe, K. 23
Varadaraj, H. 38
Varghese, T.J. 51
Veitch, P.S. 73
Vickery, C.J. 63
Vohra, R.K. 16, 75

Wahle, K.J. 7
Wakefield, C.H. 27
Wakely, C. 78
Walker, M.G. 76
Walsh, D. 47
Walsh, M. 39
Walsh, R. 65
Walters, D. 24
Waltham, M. 1
Walton, J. 62
Wang, J. 12, 7, 9
Wang, J.H. 9, 9, 9, 10, 11
Wang, Y. 19
Ward, J.B. 60
Warhurst, G. 2
Watanabe, M. 71
Watkin, D.F.L. 22, 30
Watkins, R.M. 32
Watson, A. 53
Watson, C.J.E. 48
Watson, D.I. 54, 24, 66
Watson, S.A. 1, 7
Wayman, J. 25
Webb, P. 28
Welbourn, R. 42
Weledji, E.P. 72
Wells, J.G. 60
Welsh, K.I. 48
Wencyk, P. 6
Wesnes, K. 25
Whang, E.E. 15
Wheatley, T.J. 30
Wheeler, J. 42
White, E. 56
White, K. 54
White, S.A. 19, 26, 36, 73
Whiteley, M.S. 49
Whitman, B. 63, 63
Whyman, M. 78
Widner, B. 56
Wild, C.P. 54
Wilkinson, A.R. 17
Wilkinson, M.J.S. 23
Williams, A.B. 26
Williams, N. 70
Williams, N.S. 10, 52, 69
Williams, S.B. 20
Williams, S.R. 20
Williamson, A. 28, 28
Williamson, R.C.N. 14, 14, 58, 67
Willis, A. 71
Willsher, P.C. 66
Wilmink, A.B.M. 74
Wilson, C.R. 40
Wilson, R.G. 27, 81
Wilson, V.G. 71
Wiltshire, C. 79, 79
Windsor, A.C.J. 42
Winslet, M.C. 53, 70
Wishart, G.C. 33
Witt, H. 67
Wolfe, J.H.N. 44, 63, 74
Wolowczyk, L. 17
Wood, A. 36
Woodcock, N. 30
Woodcock, N.P. 80
Wu, A. 60
Wu, Q.D. 9, 9
Wyatt, M.G. 49, 75

Yeung, S.T. 60
Yiangou, Y. 10
Youngson, G.G. 38

Zafirellis, K.D. 53, 53
Zayyan, K.S. 78
Ziprin, P. 56

British Journal of Surgery

The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Society of Academic and Research Surgeons, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

Editorial Team

Editors
J. A. Murie, *Edinburgh, UK*
J. R. Farndon, *Bristol, UK*

Associate Editors
P. J. Guillou, *Leeds, UK*
P. R. O'Connell, *Dublin, Ireland*

Website Editor
J. J. Earnshaw, *Gloucester, UK*

Statistical Consultant
G. D. Murray, *Edinburgh, UK*

Council

Chairman
R. C. G. Russell, *London, UK*

Vice-Chairman
T. Bates, *Ashford, UK*

Treasurer
N. J. McC. Mortensen, *Oxford, UK*

Company Secretary
J. R. C. Sainsbury, *London, UK*

D. Alderson, *Bristol, UK*
J. Bancewicz, *Salford, UK*
M. Büchler, *Berne, Switzerland*
V. W. Fazio, *Cleveland, Ohio, USA*
K. C. H. Fearon, *Edinburgh, UK*
I. G. Finlay, *Glasgow, UK*
(Royal College of Surgeons)
P. Lamont, *Bristol, UK*
(Surgical Research Society)
M. Lee, *Birmingham, UK*
(Association of Surgeons)
J. P. Neoptolemos, *Liverpool, UK*
H. Obertop, *Amsterdam, The Netherlands*
M. Rothmund, *Marburg, Germany*
C. J. H. van de Velde, *Leiden, The Netherlands*

Editorial Board

W. H. Allum, *UK*
C. Bassi, *Italy*
J. Beynon, *UK*
N. J. Bundred, *UK*
W. B. Campbell, *UK*
F. Castro-Sousa, *Portugal*
S. C. S. Chung, *Hong Kong*
J. D. Corson, *USA*
D. Demetriades, *USA*
D. M. Dent, *South Africa*
C. Dervenis, *Greece*
T. Diamond, *UK*
L. Fernández-Cruz, *Spain*
A. Fingerhut, *France*
O. J. Garden, *UK*
D. Gotley, *Australia*
D. J. Gouma, *The Netherlands*
P. A. Grace, *Ireland*
U. Haglund, *Sweden*
M. Kitajima, *Japan*
Z. H. Krukowski, *UK*
G. J. Maddern, *Australia*
N. Nagasue, *Japan*
A. R. Naylor, *UK*
S. Nicholson, *UK*
B. Nordlinger, *France*
L. Påhlman, *Sweden*
A. L. G. Peel, *UK*
F. Penninckx, *Belgium*
L. F. Rikkers, *USA*
B. J. Rowlands, *UK*
S. Rudzki, *Poland*
F. Seow-Choen, *Singapore*
A. Sitges-Serra, *Spain*
O. Soreide, *Norway*
R. A. J. Spence, *UK*
M. D. Stringer, *UK*
K. Sugimachi, *Japan*
J. M. Thomas, *UK*
S. Vittal, *India*
T. N. Walsh, *Ireland*
A. L. Warshaw, *USA*
S. D. Wexner, *USA*
M. H. Wheeler, *UK*

While every effort is made by the Editorial Team, members of Council and the publishers to avoid inaccurate or misleading information appearing in *BJS*, data within the individual articles and advertisements are the responsibility of the authors or advertisers concerned. The BJS Society, the publishers, and members of the Editorial Team and Council accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

The *BJS* ISSN 0007-1323

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *BJS*, Blackwell Science Ltd,
25 John Street, London WC1N 2BS, UK (Tel: +44 0207 404 1831).

Manager Elizabeth Whelan
Production Editor Emma Missen
(emma.missen@blacksci.co.uk)
Editorial Assistant Mary Savigar

Aims and scope

BJS is the premier general surgical journal in Europe and one of the top surgical periodicals in the world. Its international readership is reflected in the prestigious international Editorial Board, supported by a panel of over 1200 reviewers worldwide.

BJS features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented.

The inclusion of Leading Articles, Reviews and Original Articles means that *BJS* offers an appropriate format for any length or type of submission; in addition, there are abstracts from key meetings, correspondence and book reviews. *BJS* will be of interest not only to general surgeons, but also to specialty surgeons and those working in related fields.

Subscriptions

BJS is published monthly (one volume per annum) in 2001. Print subscription prices for 2001 are:

	EUROPE	REST OF WORLD	NORTH AMERICA
Institutional	£146.00	£169.00	$261.00
Individual	£87.00	£101.00	$156.00
All Trainee Surgeons UK and ASIT			
	£43.50	£50.50	$78.50
Surgeons in Training Worldwide			
	£43.50	£50.50	$78.50

For online access in addition to print, please add 10 per cent to the print subscription price. For an online subscription without a print subscription, please pay 90 per cent of the print subscription price.

All members of the Association of Surgeons of Great Britain and Ireland, Surgical Research Society and Association of Surgeons of the Netherlands receive the paper journal as a benefit of membership of the society. In addition, all members have full access to the online version of the journal.

Subscribers in Canada must add 7% to the subscription price to allow for GST. Subscribers in Europe must quote their VAT registration number or state that they are not registered. Subscribers in the following countries who are not VAT-registered must add VAT at the appropriate rate:

Belgium (6% TVA/BTW)
France (2.1% TVA)
Germany (7% MWST)
Spain (4% IVA)
The Netherlands (6% BTW)

Orders for current subscriptions and back issues should be sent to Blackwell Science Ltd, Journal Subscriptions, PO Box 88, Oxford OX2 0NE, UK. Tel: +44 1865 206180; Fax: +44 1865 206219; e-mail: jnl.orders@blacksci.co.uk

Despatch

BJS is despatched within the UK by second class post, within Europe by air mail, and to other continents by various forms of air-speeded delivery, to the USA by air freight for forwarding by second class post*, to India by air freight for guaranteed local delivery, and to all other countries by accelerated surface post. Add to the cost of a regular subscription £24.00/$36.00 for air mail delivery outside Europe.

Business correspondence

All other business correspondence, including orders for offprints (offprints@blacksci.co.uk) and advertising space (advert@blacksci.co.uk) should be addressed to:
BJS, Blackwell Science Ltd, Osney Mead,
Oxford OX2 0EL, UK. (Tel. +44 1865 206206;
Fax: +44 1865 721205).

Copyright and photocopying

© 2001 Blackwell Science, acting as agents for the BJS Society. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Science for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $15 per copy is paid directly to CCC, 222 Rosewood Drive, Suite 910, Danvers, MA 01973, USA. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to the publisher.

Paper

The Publisher's policy is to use acid-free permanent paper, to the draft standard ISO/DIS/9706, made from sustainable forests using chlorine-free pulp. The paper used in this journal has an ECO-CHECK 4-star rating.

BJS has a worldwide website at: http://www.bjs.co.uk

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the publisher.

Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

Hands-on practice in the OR is an effective way of building laparoscopic surgery skills. But there is one problem: with a live patient on the table, learning by trial-and-error is simply not an option. But now, there is a safe and effective alternative.

A training aid that really works

LapSim Basic Skills™ 1.0 is a digital training aid that replaces the vulnerable patient with expendable pixels. By digitally recreating the procedures and environment of abdominal keyhole surgery, LapSim provides an effective learning experience.

Studies support our claims. Novice surgeons trained using LapSim acquire skills that actually transfer into the OR.[1] With LapSim, the digital laparoscopic simulation system has come of age.

Quality Assurance

As the screenshot above shows, high-resolution 3D graphics provide relevant visual input. But that's not all.

Using LapSim Basic Skills, quality assurance may be introduced into laparoscopy training. As the resident progresses through the training program, all results are carefully monitored and stored. Each junior surgeon can be individually provided with as much training as is necessary in order to reach a certain proficiency level. Certified laparoscopy training is just around the corner.

lap sim®
LAPAROSCOPIC SIMULATION
BASIC SKILLS

An expanding system

The initial version of LapSim contains five training tasks, from camera navigation to basic cutting. Being a modular system, it will be continually expanded and improved upon. Upgrades are already in the pipeline. Surgical Science is committed to providing training tools that allow surgeons at all levels to practice and gain experience in a safe way. LapSim Basic Skills 1.0 is just the beginning.

More information? Please visit www.surgical-science.com, or contact us directly.

---

[1] Abstract EAES Maastricht June 2001. Please visit our website for more information

OUR MISSION IS
SAFER
SURGEONS
FASTER

surgicalscience

Haraldsgatan 5, SE 413 14 Göteborg, Sweden. Tel +46 31 741 65 60 info@surgical-science.com WWW.SURGICAL-SCIENCE.COM

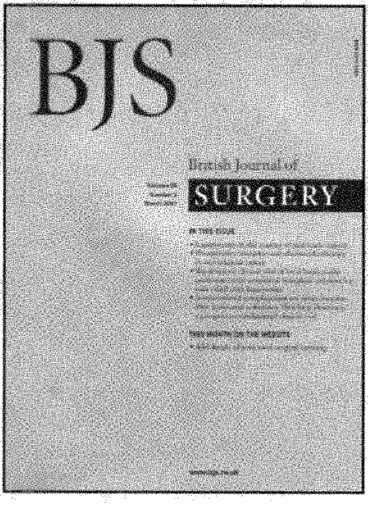
b
Blackwell
Science

BJS

British Journal of
SURGERY
now available online *through*
Blackwell *Synergy*

Visit *BJS* online FREE

Simply register at www.blackwell-synergy.com to:



◆ *Select* tables of contents emailed directly to your desktop, keeping you up-to-date with the latest publications in the field

◆ *Browse* through all tables of contents and article abstracts, and save favourites in your personal *Synergy* homepage

◆ *Search* by phrase, keyword, author, or title within full text articles for the information you need

◆ *Access* free sample issues

Subscribe to *BJS* and you will also be able to:

◆ *Choose* articles in full-text HTML, with embedded links, high quality figures and tables, or in PDF format, excellent for printing

◆ *Link* directly from references, authors and keywords to MEDLINE, and to cited articles in other journals

◆ *Save* articles to disk for your own research and for copying for course packs

◆ *Read* articles from all available online back volumes

If you are a member of the *Association of Surgeons, Surgical Research Society* or the *Association of Surgeons of the Netherlands*, you are entitled to access *BJS* online as part of your member benefits.

All qualifying members will be contacted by the Society or by Blackwell Science with instructions on how to access the journal on *Synergy*. If you are a member and would like help accessing *BJS* online, please contact Journal Customer Services on tel: +44 (0)1865 206126.

Your institution may already have a subscription to the online version of *BJS*. Simply ask your library administrator.

You can upgrade your Print Subscription to include the Online Version for just 10% extra, or subscribe to Online Only and save 10%.

Synergy
Blackwell
Online Journals

Contents

British Journal of Surgery

Volume 88, Issue 10, October 2001

Leading articles

1281 **Endovascular treatment of abdominal aortic aneurysm: a failed experiment**
J. Collin and J. A. Murie
A challenge to endovascular surgeons

1283 **Ethics of consent to surgical treatment**
T. Bates
Reflections on the plethora of available advice

Systematic review

1285 **Systematic review of randomized clinical trials of surgical treatment for carpal tunnel syndrome**
A. A. M. Gerritsen, B. M. J. Uitdehaag, D. van Geldere, R. J. P. M. Scholten, H. C. W. de Vet and L. M. Bouter
The standard open operation remains the preferred method

Reviews

1296 **Effect of laparoscopy on immune function**
A. Gupta and D. I. Watson
The systemic benefits of laparoscopic surgery may not extend to the peritoneal interface

1307 **Detection and clinical significance of occult tumour cells in colorectal cancer**
G. Tsavellas, H. Patel and T. G. Allen-Mersh
The future potential of molecular assays is explored

Randomized trial

1321 **Randomized clinical trial comparing suture and mesh repair of umbilical hernia in adults**
A. Arroyo, P. García, F. Pérez, J. Andreu, F. Candela and R. Calpena
Mesh repair may become standard

Association of Surgeons

1324 **Extent of ductal carcinoma *in situ* within and surrounding invasive primary breast carcinoma**
N. Crombie, R. S. Rampaul, S. E. Pinder, C. W. Elston, J. F. R. Robertson and I. O. Ellis
Extensive ductal carcinoma *in situ* outside the invasive tumour is of prognostic importance

1330 **Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients**
G. Libertiny, C. J. E. Watson, D. W. R. Gray, K. I. Welsh and P. J. Morris
Rising incidence is independent of cyclosporin

1335 **Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm**
T. E. Rowlands and S. Homer-Vanniasinkam
Cytokine imbalance may be responsible for greater morbidity after open repair

1341 **Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre**
K. Cassar, D. J. Godden and J. L. Duncan
A study from a large, sparsely populated region

1344 **Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note)**
B. Neary, B. Whitman, C. Foy, B. P. Heather and J. J. Earnshaw
POSSUM in a non-surgical setting

Imperial College School of Medicine
Postgraduate Short Courses

Annual Course in Hepatobiliary and Pancreatic (HPB) Surgery

5 - 6 November 2001

This two-day course will cover recent advances in the management of patients with benign and malignant diseases of the liver, biliary tract and pancreas and will include multidisciplinary symposia and lectures on pancreatic carcinoma, biliary strictures, liver transplantation and liver cancer.

Invited speakers include:

Professor D Castaing
Mr N A Habib
Professor W Holtkamp
Dr J E Jackson
Professor D Jaeck
Mr A K Kakkar
Professor G Nuzzo
Professor E Papavangelou
Dr P Tait
Professor R C N Williamson

Course organisers: Mr N A Habib, Mr A K Kakkar, Professor R C N Williamson

Course fee: **£50.00** (including catering)

Further details from:
Wolfson Conference Centre
Imperial College School of Medicine
Hammersmith Hospital
Du Cane Road
London W12 0NN

Tel: +44 (0)20 8383 3117/3227/3245
Fax: +44 (0)20 8383 2428
Email: wcc@ic.ac.uk

http://www.med.ic.ac.uk/divisions/cc/wolfson.asp

Application for CME recognition will be made

SURGICAL SKILLS UNIT

Fistula-in-ano Course

19th December 2001 **Fee: £150**

Faculty: **Professor Robin Phillips, London**
Professor Robert Steele, Dundee
Mr Mike Lavelle-Jones, Dundee
Mr Ken Campbell, Dundee
Mr Declan Shepherd, Dundee

This course is designed for higher surgical trainees and consultants with an interest in coloproctology. It consists of live operating to demonstrate the surgical management of the difficult fistula and discussion fora on the aetiology, anatomy and treatment of fistulous diseases. There will also be opportunities to discuss individual cases.

Course fee includes tuition, workbook, materials and lunch

Call Unit for further details

MINIMAL ACCESS THERAPY TRAINING UNIT SCOTLAND

Contact: Mrs A Duncan
Surgical Skills Unit
Level 5,
Ninewells Hospital and Medical School,
Dundee, DD1 9SY
Tel. 01382 645857
Fax 01382 646042
http://www.dundee.ac.uk/surgicalskills

UNIVERSITY OF DUNDEE

---

b Blackwell Science

reprints
Blackwell Science

of articles for the healthcare industry

Reprints of articles in this journal can be purchased from Blackwell Science Ltd, for use by the healthcare industry. Relevant articles on your products, or therapeutic areas, can help your intended market as well as company colleagues.

Articles can be supplied with a plain cover or the cover from the journal (and it may be possible to include your own advertising).

Further details and quotations (on order quanitities of 500 and above) for a fast efficient service can be obtained from:

Julie Joyner
Offprints manager
Blackwell Science Ltd
Osney Mead, Oxford OX2 0EL
Tel: +44 (0)1865 206152
Fax: +44 (0)1865 206189
email:julie.joyner@blacksci.co.uk

Stephanie Wenzel
Special sales department
Blackwell Wissenschafts-Verlag Gmbh
Kurfürstendamm 57
D-10707 Berlin
Tel: 030 327 90651
Fax: 030 327 90686
email:swenzel@blackwis.de

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder

FELLOWSHIP OPPORTUNITY
PEDIATRIC SURGICAL ONCOLOGY

The Department of Surgery at St. Jude Children's Research Hospital is offering a Fellowship in Pediatric Surgical Oncology. Eligible candidates should have completed either a general surgical residency program or a pediatric surgical training program or its equivalent. This Fellowship will be tailored to the needs of the candidate, but will include clinical training in the care of children with a variety of childhood malignancies as well as experience in clinical and basic research. The Fellowship will be for one year with an option to gain additional laboratory experience during a second year. Depending upon the experience of the candidate, arrangements can be made to spend three months of the first year participating in the care of adult surgical oncology patients with an emphasis on gaining additional experience in specific areas such as head and neck surgery and the management of adult sarcoma. Training in the use of advanced minimally invasive surgical techniques in children is also available depending upon the interest of the candidate.

Applicants should submit a curriculum vitae to: **Stephen J. Shochat, M.D., Chairman, Department of Surgery, St. Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38105. Ph: 901-495-2911; Fax: 901-495-2207.** EOE/MN/DN

www.stjude.org

1346 **Diagnosis and management of a mediastinal leak following radical oesophagectomy**
S. M. Griffin, P. J. Lamb, S. M. Dresner, D. L. Richardson and N. Hayes
A study of 19 leaks after 291 operations

1352 **Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer**
A. I. Sarela, J. A. Guthrie, M. T. Seymour, E. Ride, P. J. Guillou and D. S. O'Riordain
Role for non-operative management

1357 **Prevention of the neoplastic progression of Barrett's oesophagus by endoscopic argon beam plasma ablation**
C. D. Morris, J. P. Byrne, G. R. A. Armstrong and S. E. A. Attwood
No malignant complications in this series of ablations supports its use in preventing oesophageal carcinoma

1363 **Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery**
G. Sanders, S. J. Mercer, K. Saeb-Parsy, M. A. Akhavani, K. B. Hosie and A. W. Lambert
Bowel preparation causes dehydration

Original articles

1366 **Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation**
F. Pi, F. Badosa, A. Sola, J. Roselló Catafau, C. Xaus, N. Prats, E. Gelpí and G. Hotter
Adenosine may induce an inflammatory response after reperfusion

1376 **Reintervention as a clinical trial endpoint after peripheral arterial bypass surgery**
H. R. Watson, G. Belcher and M. Horrocks
A new way of reporting bypass graft trials

1382 **Outcome of surgical treatment for carotid body paraganglioma**
J. T. M. Plukker, E. P. Brongers, A. Vermey, A. Krikke and J. J. A. M. van den Dungen
An experience of 45 tumours

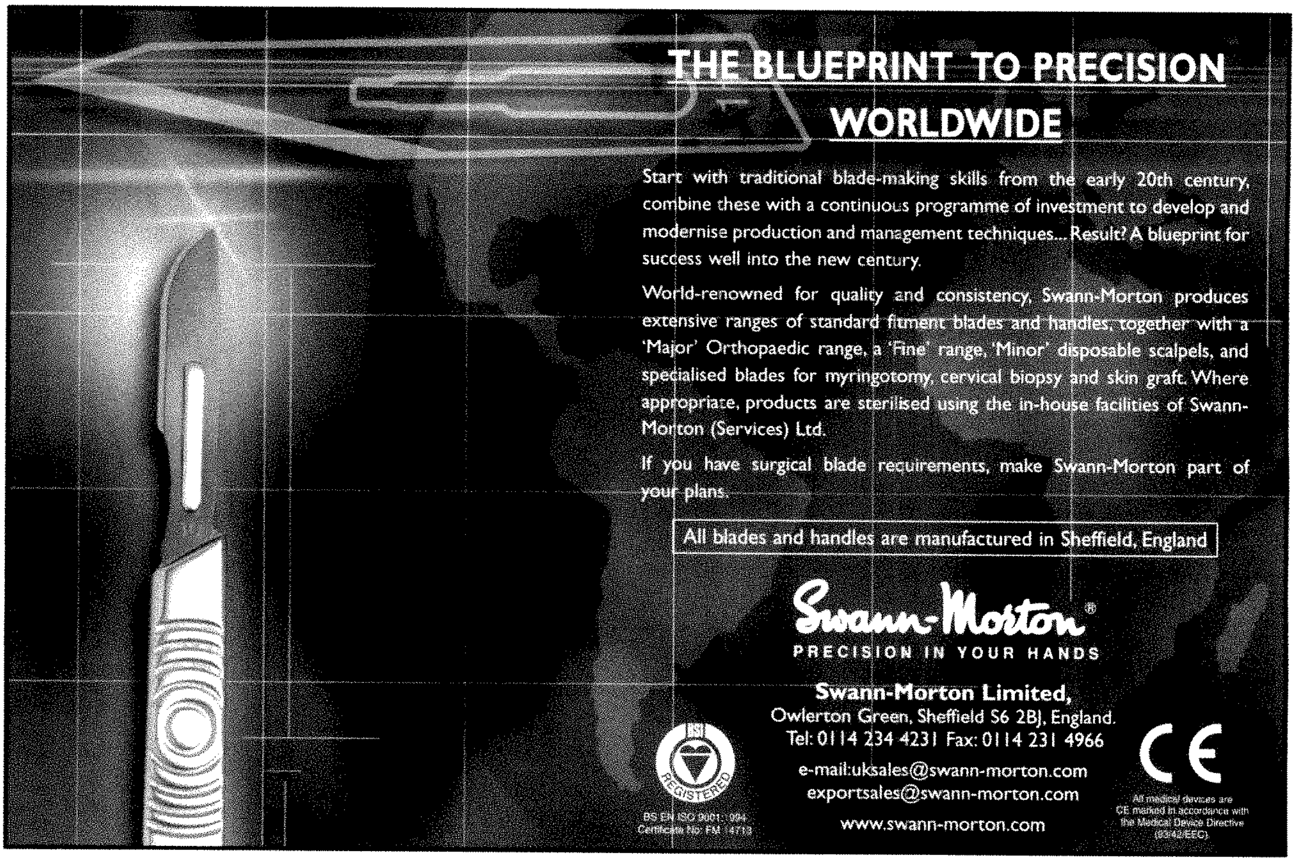
1387 **Small bowel obstruction after appendicectomy**
R. E. B. Andersson
The risk is low

1392 **Strategy for the surgical management of patients with idiopathic megarectum and megacolon**
C. B. Ó Súilleabháin, J. H. Anderson, R. F. McKee and I. G. Finlay
Colonic motility studies may aid choice of surgical procedure

1397 **Hospital caseload and the results achieved in patients with rectal cancer**
F. Marusch, A. Koch, U. Schmidt, M. Pross, I. Gastinger and H. Lippert
Caseload effects outcome

1403 **Prospective controlled trial of a standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1**
P. Langer, A. Wild, I. Celik, I. Kopp, A. Bergenfelz and D. K. Bartsch
Meal stimulation test has been superceded

1408 **Influence of the number of lymph nodes examined on staging of gastric cancer**
H. K. Lee, H.-K. Yang, W. H. Kim, K. U. Lee, K. J. Choe and J.-P. Kim
The higher the T stage, the more lymph nodes are needed



THE BLUEPRINT TO PRECISION WORLDWIDE

Start with traditional blade-making skills from the early 20th century, combine these with a continuous programme of investment to develop and modernise production and management techniques... Result? A blueprint for success well into the new century.

World-renowned for quality and consistency, Swann-Morton produces extensive ranges of standard fitment blades and handles, together with a 'Major' Orthopaedic range, a 'Fine' range, 'Minor' disposable scalpels, and specialised blades for myringotomy, cervical biopsy and skin graft. Where appropriate, products are sterilised using the in-house facilities of Swann-Morton (Services) Ltd.

If you have surgical blade requirements, make Swann-Morton part of your plans.

All blades and handles are manufactured in Sheffield, England

Swann-Morton®
PRECISION IN YOUR HANDS

Swann-Morton Limited,
Owlerton Green, Sheffield S6 2BJ, England.
Tel: 0114 234 4231 Fax: 0114 231 4966
e-mail:uksales@swann-morton.com
exportsales@swann-morton.com
www.swann-morton.com

REGISTERED
BS EN ISO 9001: 994
Certificate No: FM 14713

All medical devices are CE marked in accordance with the Medical Device Directive (93/42/EEC).

TO ADVERTISE IN THIS JOURNAL CONTACT:

Katrina Erskine

Tel: + 44 (0) 1865 206238 or Fax: +44 (0) 1 865 206189
Email: katrina.erskine@blacksci.co.uk

Or access our website for further information:
http://www.blackwell-science.com

b
Blackwell Science

Blackwell Science Ltd, Osney Mead, Oxford, OX2 0EL, UK

1413 **Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark**
T. Filtenborg Tvedskov, M. S. Rasmussen and P. Wille-Jørgensen
Still considerable variation in Denmark

1417 **Correspondence**

1420 **Book reviews**

1422 **Scientific surgery**

1423 **Instructions to authors**

0007-1323(200110)88:10;1-E

b

Blackwell Science

Osney Mead
Oxford
OX2 0EL
UK

Tel:
+44 (0) 1865 206097

Fax:
+44 (0) 1865 206026

www.medirect.com

~

2 Commerce Place
350 Main St
Malden
MA
02148 USA

Tel:
1 781 388 8250

Fax:
1 781 388 8255

www.
blackwellscience.com

Textbook of Surgery

NEW! Second Edition

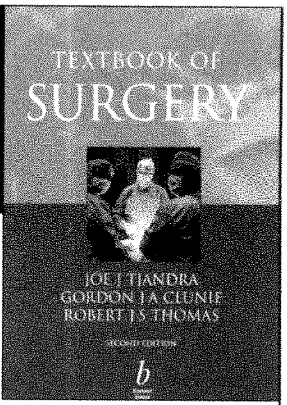
Joe J. Tjandra, Gordon J. A. Clunie and
Robert J. S. Thomas

This book approaches surgery from a practical viewpoint while emphasing the relevance of basic surgical principles. Most aspects of general surgery and selected topics of specialty surgery, including cardiothoracic surgery, neurosurgery, plastic surgery and orthopaedic surgery have been covered. Principles that underlie the assessment, care and treatment of surgical patients are outlined, followed by sections on various surgical disorders. This book presents problem solving approaches to the diagnosis and management of common surgical conditions.

All information is presented in a concise fashion with an attractive and easily readable format using tables, boxes and illustrations. Important leading references of classic publications or up-to-date literature have been provided at the end of each chapter.

All contributors to this book have been carefully chosen for their authoritative expertise and personal involvement in undergraduate and postgraduate teaching, and each topic is written by an expert in the field from his own wisdom and experience.

ISBN 0867930233, 500 pages, illustrated paperback, April 2001, 29.50



Pocket Diagnosis in General Surgery

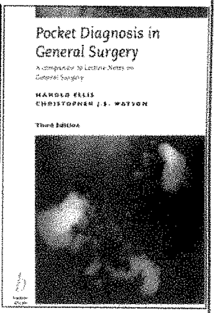
Third Edition

Harold Ellis and Christopher J. E. Watson

Pocket Diagnosis in General Surgery is an essential self-assessment guide offering a concise revision course in surgery. Extensively updated since the second edition, the revised book features a series of cases presented as a photograph with brief history, followed by a series of questions designed to test the reader's skills of diagnosis and management. In this new edition, a whole new section of case history problems and their solutions has been added, making this an essential purchase for those facing their surgery finals.

Pocket Diagnosis in General Surgery is a companion text to *Lecture Notes in General Surgery* and has been designed as a resource for study and is handily-sized for quick reference in the clinical setting.

ISBN 0632054794, 320 pages, illustrated paperback, April 2001, £16.95

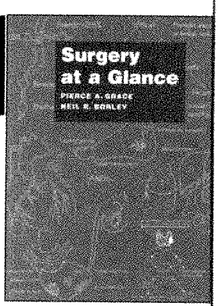


Surgery at a Glance

Pierce A. Grace and Neil R. Borley

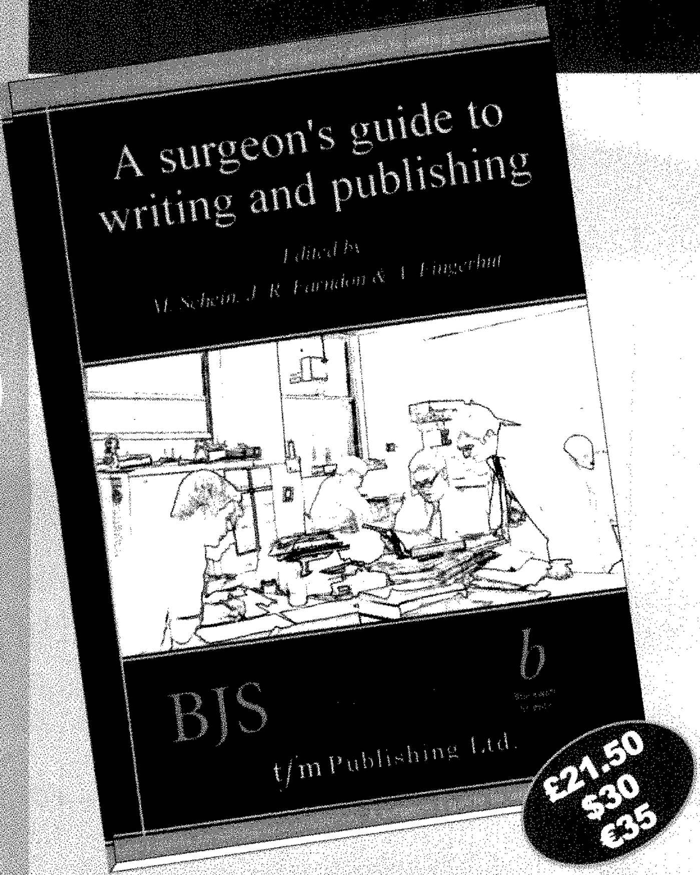
Surgery at a Glance aims to present surgical and clinical presentations in the easy to use, revision aid formula for which the *at a Glance* series is well known. Starting with acute and emergency presentations, **Surgery at a Glance** guides the student through surgical procedures system by system. Each page of text is accompanied by a page of illustration which will aid both diagnosis and management.

ISBN 0632049588, 176 pages, illustrated paperback, February 1999, £12.95



All you ever wanted to know about publishing but never dared to ask.

Publication date September 200


A surgeon's guide to writing and publishing
Edited by
M. Schein, J. R. Farndon & A. Fingerhut
BJS
b
tfm Publishing Ltd.

£21.50
$30
€35

Edited by

M. Schein *Professor of Surgery, Cornell University Medical College and Bronx Lebanon Hospital, New York, U.S.A.*

J. R. Farndon *Professor and Head of Division, University of Bristol and Consultant Surgeon, Bristol Royal Infirmary, Bristol, UK.*

A. Fingerhut *Chief of Service, Digestive Surgery, Centre Hospitalier Intercommunal, Poissy, France and Associate Professor of Surgery, Louisiana State University Medical School, New Orleans, LA, U.S.A.*

Includes over 30 contributions from leading surgical authors, many of whom are editors of renowned surgical journals.

Contents

Why should a surgeon publish? • What should surgeons write? • Where can the surgeon publish? • Generating an idea: will it be publishable? • On getting started • Writing a manuscript • Advice on writing style • The 'foreign' author • Essential statistics • Writing about a surgical technique • The final product • What an editor wants or expects from authors • How to write a chapter • How to edit or write a book • How to write a commentary • On the editor's desk • Politics in surgical publishing • Dealing with the rejected article • Research misconduct: diagnosis, treatment and prevention • Internet communication and e-publishing • Epilogue: key considerations in surgical publishing

You are familiar with the wisdom of 'publish or perish' and you perceive that it might be advisable for you to follow this maxim but you do not know how to begin.

Having been in your shoes only a few years ago the editors of this book know exactly how you feel. Let 'A surgeon's guide to writing and publishing' be your guide.

After reading this book you should be better informed and successful in writing, publishing and editing. You will be ready to 'publish and not be damned'.

ISBN 1 903378 01 X, 298pp soft-back, 149mm x 210mm

ORDER YOUR COPY NOW (GBP £25; USD $37; EUR €43 incl. p&p)

Please supply __copy/copies of 'A surgeon's guide to writing and publishing'

Name .... Tel no ....

Address ....

....

Card no. .... Exp. date .... Issue no. ...... Signature ....

Visa/Mastercard/Switch/Solo/American Express/cheque

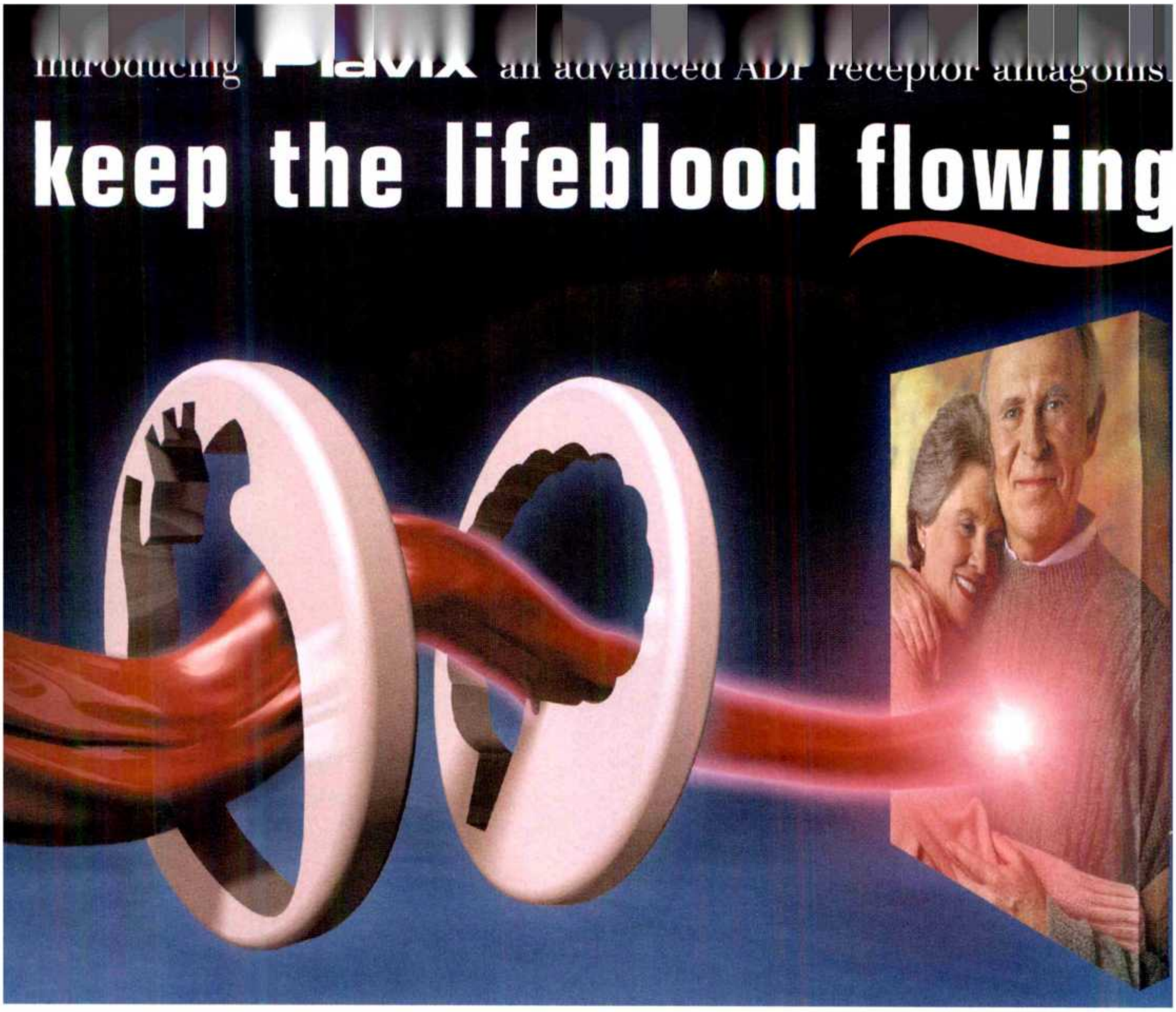
Order by mail, 'phone or fax

USA and Canada:

tfm Publishing Ltd, c/o MPHC, 870 Market Street, San Francisco, CA 94102, USA. Tel 1-800-658-8820, Fax 1-415-362-2333

Elsewhere:

tfm Publishing Ltd, Brimstree View, Kemberton, Shropshire, TF11 9LL, U.K. Tel +44 (0)1952 586408, Fax +44 (0)1952 587654


Introducing Plavix an advanced ADP receptor antagonis
keep the lifeblood flowin

Introducing PLAVIX - the first drug specifically designed for, and proven in, the prevention of further ischaemic events: MI, STROKE and VASCULAR DEATH.*

In a trial against aspirin in over 19,000 recent MI, recent ischaemic stroke and atherosclerotic PVD patients, PLAVIX was proven to be significantly more effective at reducing further events: MI, STROKE and VASCULAR DEATH.[1]*

*CAPRIE[1]: comparison of efficacy of clopidogrel versus aspirin; Inclusion criteria: patients with ischaemic stroke (from 7 days to less than 6 weeks), MI (less than 35 days) or established peripheral vascular disease; Endpoint: Combined endpoint o MI, ischaemic stroke, vascular death for the overall population

Plavix®
clopidogrel 75mg

PREVENTING VASCULAR EVENTS

sanofi

Bristol-Myers Squib

PRESCRIBING INFORMATION
PRESENTATION: Round, pink, film coated tablets containing 75 mg clopidogrel (as the bisulphate). INDICATION: Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days), or established peripheral arterial disease. DOSAGE: Adults and elderly: 75 mg as a single daily dose. Children and adolescents: Not recommended under 18 years. CONTRAINDICATIONS: Hypersensitivity to clopidogrel or excipients; severe liver impairment; active pathological bleeding; breast-feeding. WARNINGS: Caution in patients at increased bleeding risk; patients with lesions likely to bleed, particularly gastrointestinal or intraocular; renal impairment; hepatic disease. Not recommended during pregnancy. DRUG INTERACTIONS Not recommended with warfarin. Caution with aspirin, NSAIDs, heparin, thrombolytics SIDE EFFECTS: Haemorrhagic disorders; haematological including bleeding such a bruising, haematoma, and epistaxis; gastrointestinal including diarrhoea; rash. LEGA CATEGORY: POM. PRODUCT LICENCE NUMBER: EU/1/98/069/001. MARKETIN AUTHORISATION HOLDER: Sanofi Pharma Bristol-Myers Squibb SNC. FURTHE INFORMATION is available from: Sanofi Winthrop Ltd, One Onslow Street, Guildford Surrey, GU1 4YS. Tel: 01483 505515. Fax: 01483 535432. BASIC NHS PRICE: £35.3 for 28 tablets. Date of preparation: November 1999. Reference: 1. CAPRIE Steerin Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at ris of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339.

PLA-99/231J

Leading article

Endovascular treatment of abdominal aortic aneurysm: a failed experiment

J. Collin and J. A. Murie*

Nuffield Department of Surgery, John Radcliffe Hospital, Oxford OX3 9DU (e-mail: jack.collin@nds.ox.ac.uk) and *Department of Vascular Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK

Abdominal aortic aneurysms (AAAs) smaller than 55 mm in maximum anteroposterior diameter, as measured by ultrasonography, have a rupture rate of no more than 1 per cent per annum[1]. Despite various speculative calculations, the rupture rates for larger aneurysms are still unknown. Conventional (open) transabdominal surgical repair of an AAA carries a true overall operative mortality rate of about 8 per cent, but most major vascular surgical centres claim rates of less than 5 per cent. The trade-off between immediate operative death and fortuitous death from aneurysm rupture is perplexing. Elective repair is usually recommended for aneurysms greater than 55 mm in diameter. Patients who survive open AAA surgery have a residual lifetime risk of death from prosthetic infection, aortoenteric fistula, and anastomotic and new aneurysm rupture that is unknown but probably less than 10 per cent.

Endovascular repair of AAA was first attempted by Parodi in Argentina in 1991. In the intervening 10 years a plethora of customized and commercial prostheses has been deployed in thousands of patients around the world. Proprietary devices have promptly been withdrawn as appliance failures ensued – some to be redesigned, reintroduced and recalled again. No prosthesis has remained in continuous unmodified use for long.

The technical feasibility of endoluminal AAA repair decreases with increasing aneurysm diameter. In published series aneurysm diameters have often been reported (inappropriately for non-parametric data) as mean values; median diameters have not been disclosed, perhaps advisedly. The aneurysm diameters in large series suggest that at least half of the aneurysms subjected to endovascular operation have been less than 55 mm in diameter, as measured by computed tomography (CT)[2,3]. Some series from individual centres contain an even greater proportion of small aneurysms[4]. The CT measured any plane diameter is usually greater than the ultrasonographically measured maximum anteroposterior diameter. A majority of endovascular AAA operations performed to date have probably been in patients who had an annual risk of aneurysm rupture of less than 1 per cent.

The overall operative mortality rate attributable to endovascular AAA surgery is unknown. Many more prostheses have been sold than can be accounted for in voluntary operation registers; compulsory preprocedure registration and totally independent audited follow-up are glaring omissions. Single-centre reports by enthusiasts are well known to paint an overoptimistic picture, and this, combined with reporting and publication bias, suggests strongly that published results provide flawed guidance.

The small AAAs most suited to endovascular repair are those that are easiest to repair by conventional methods, and there is no reason to suppose that the primary operative mortality rate of the two techniques is substantially different. Within 1 month of endoluminal AAA repair, 2–16 per cent of patients require conversion to open operation and further conversions accrue as follow-up continues; the operative mortality rate associated with such complex secondary surgery is 18–27 per cent[5]. The common complications of endovascular repair include various kinds of endoleaks and kinking, misplacement and migration of the graft. Such problems are frequently treated in the perioperative period but they continue to arise during follow-up, with more than 20 per cent of patients requiring reintervention by 1 year. A recent communication, which specifically excluded secondary interventions in the first month of follow-up, has documented a subsequent need for reintervention of 10 per cent per annum for up to 4 years after the primary procedure[6].

The costing of surgical procedures is almost always inexact, but a typical endovascular AAA repair has a perioperative cost of over £7000, compared with approximately £5000 for an open repair[7]. For endovascular repair there are in addition the costs of obligatory lifetime surveillance with CT, ultrasonography and/or angiography, and the lifelong contingent liability for endovascular reintervention and eventual complicated open surgical repair. In Australia the surgeon's fee for a typical open AAA repair is currently about £425, whereas that for endovascular repair is £970; secondary endovascular and open interventions attract additional remuneration. The economic impact alone of endovascular AAA repair will render its widespread acceptance improbable[7].

After endovascular surgery, if there are no endoleaks, AAAs usually either shrink in size or show no change in diameter. It is possible that such aneurysms are at less risk of rupture than before the intervention. In contrast, when endoleaks are present, whether they are overt or occult, continued expansion usually occurs and the risk of rupture may be increased by the presence of a dysfunctional graft. The reported rupture risk of 1 per cent per annum following the insertion of an endoluminal prosthesis is the same as the natural history of the disease for the majority of the aneurysms so treated[8,9]. Some surgeons have suggested that endovascular treatment of AAAs may have an application in patients unfit for elective open surgery. The mortality rate following such intervention is 6–16 per cent at 30 days and 20–30 per cent at 12 months[10,11]. In comparison, the small risk of aneurysm rupture without treatment and the possible reduction in rupture risk following successful endoluminal repair pale into insignificance.

Endovascular surgery is an irresistible lure for vascular surgeons and interventional radiologists. It is new, exciting, high profile and fashionable. Manufacturers of stent-graft prostheses and surgeons anxious not to miss the boat or to appear antiquated have rushed devices out of the factory and into the patient. Few academic surgical departments with any pretension to be abreast of events have been able to resist the tide. Personal and institutional prestige, and sometimes more perverse professional and financial incentives, have contributed to the large number of endovascular operations. To secure valid consent, a surgeon is ethically obliged to ensure that the patient has had the opportunity to consider all relevant information on the risks, as well as the benefits, of an intervention, and any alternative operative and conservative treatments must be discussed. The authors certainly would not consent to endovascular AAA repair and are astonished that so many patients have.

References

1 UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998; **352:** 1649–55.

2 Buth J, Laheij RJF, Parodi JC, the EUROSTAR Collaborators. Early complications and endoleaks after endovascular abdominal aortic aneurysm repair: report of a multicenter study. *J Vasc Surg* 2000; **31:** 134–46.

3 May J, White GH, Waugh R, Stephen MS, Chaufour X, Arulchelvam M *et al.* Comparison of first- and second-generation prostheses for endoluminal repair of abdominal aortic aneurysms: a 6-year study with life table analysis. *J Vasc Surg* 2000; **32:** 124–9.

4 Becquemin J, Bourriez A, D'Audiffret A, Zubilewicz T, Kobeiter H, Allaire E *et al.* Mid-term results of endovascular *versus* open repair for abdominal aortic aneurysm in patients anatomically suitable for endovascular repair. *Eur J Vasc Endovasc Surg* 2000; **19:** 656–61.

5 Cuypers PWM, Laheij RJF, Buth J. Which factors increase the risk of conversion to open surgery following endovascular abdominal aortic aneurysm repair? The EUROSTAR Collaborators. *Eur J Vasc Endovasc Surg* 2000; **20:** 183–9.

6 Laheij RJF, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven ELG. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European Collaborative Registry (EUROSTAR). *Br J Surg* 2000; **87:** 1666–73.

7 Clair DG, Gray B, O'Hara PJ, Ouriel K. An evaluation of the costs to health care institutions of endovascular aortic aneurysm repair. *J Vasc Surg* 2000; **32:** 148–52.

8 Harris PL, Vallabhaneni SR, Desgranges P, Becquemin JP, van Marrewijk C, Laheij RJF. Incidence and risk factors of late rupture, conversion, and death after endovascular repair of infrarenal aortic aneurysm: the EUROSTAR experience. *J Vasc Surg* 2000; **32:** 739–49.

9 May J, White GH, Waugh R, Chaufour X, Stephen MS, Yu W *et al.* Rupture of abdominal aortic aneurysms: a concurrent comparison of outcome of those occurring after endoluminal repair *versus* those occurring *de novo*. *Eur J Vasc Endovasc Surg* 1999; **18:** 344–8.

10 Laheij RJF, van Marrewijk CJ. Endovascular stenting of abdominal aortic aneurysm in patients unfit for elective open surgery. EUROSTAR Group. *Lancet* 2000; **356:** 832.

11 Walker SR, Macierewicz J, MacSweeney ST, Gregson RH, Whitaker SC, Wenham PW *et al.* Mortality rates following endovascular repair of abdominal aortic aneurysms. *J Endovasc Surg* 1999; **6:** 233–8.

If you wish to comment on this, or any other article published in the *BJS*, please visit the on-line correspondence section of the website (www.bjs.co.uk). Electronic communications will be reviewed by the Correspondence Editor and a selection will appear in the correspondence section of the Journal.

Leading article

This is the eighth in a series of articles on ethics, professional governance and the law that BJS will run through the remainder of 2001.

Ethics of consent to surgical treatment

T. Bates

Breast Unit, William Harvey Hospital, Kennington Road, Willesborough, Ashford TN24 0LZ, UK (e-mail bates.tom@virgin.net)

The ethical issues of consent to surgical treatment have become inextricably linked with the law. The Human Rights Act 1998, which came into force in England and Wales in October 2000, threatens further uncertainty in an already confused area[1]. In the UK the recommendations of the Senate of Surgery[2] led to the position paper on consent to treatment (1998) from the General Medical Council (GMC)[3] and has been followed by the recent publication of advice from the Department of Health[4] and the British Medical Association[5]. Health authorities and malpractice insurers[6,7] have also been active in the issue of instructions, guidelines and protocols for consent to surgical treatment. This plethora of advice has an ethical preamble but has largely arisen in a setting of damage limitation and cost containment, in an attempt to stem the rising tide of litigation for medical malpractice. As yet there is no evidence that this activity has been effective, but there now seems to be a redoubling of effort.

For consent to be valid, a patient must be competent to make the necessary decision, be provided with sufficient information and act voluntarily[8], but his or her mental capacity may require a difficult value judgement on the part of the surgeon. In English law no-one other than an adult person can give consent to his or her own treatment but in the intensive care unit, when a patient is unconscious, it is wise to consult the relatives to obtain their assent to any treatment plan[2]. The concept of informed consent was well described by Lord Scarman in his minority opinion in the Sidaway case[9] but the legal requirement for such consent has long been accepted in North America[10]. From an ethical standpoint informed consent, which encompasses disclosure of significant risk and alternative management, is generally agreed to be an essential prerequisite to surgical intervention. There is, however, often a yawning gap between good intentions and the reality of day-to-day practice. It is recognized that a change of culture is required to ensure that patients become informed partners in their own care[3], but this will also require a better public understanding of the nature of risk. It is not unusual at a postoperative consultation for a patient to express surprise that a complication of which he or she was warned has not arisen. It is only then apparent that the patient has been made unnecessarily fearful of a rare adverse event.

The GMC exhorts clinicians to 'find out the patient's individual needs and priorities ... beliefs and culture' when providing information about treatment and options[3], but this is a very exacting standard. That patients should be advised 'in a form they can understand' requires a value judgement that is difficult but critical to the validity of consent. Verbal consent in medicolegal actions will always be challenged since the recollection of the surgeon is usually preceded by the rather unconvincing statement that 'I would have said' or 'I always warn'. This has led to an increasing reliance on hand-written additions to the printed consent form to accentuate and confirm that appropriate verbal information was indeed given.

Faced with a specific enquiry from a patient about the number of operations carried out in a unit and the likely outcome, the surgeon may be inclined to guess (and furthermore to underestimate the risk and overestimate previous experience and the potential benefit of the procedure). Until recently this would have been considered a relatively benign or even benevolent trait in reassuring patients and their relatives but it is now branded paternalistic. The recent troubles within the cardiac surgery unit of Bristol Royal Infirmary have proved cataclysmic. For a colleague to be struck off the medical register for, *inter alia*, giving parents a serious underestimate of risk from paediatric cardiac surgery will surely concentrate the mind of surgeons. It might be argued convincingly that a specialist unit should have up-to-date and accurate audit data of outcome. A traditional general surgery operating list, however, may encompass four or five procedures on different parts of the body for which the specific risks of each can be described only imprecisely. At an apparently mundane level a patient may wish to know the risk of complications after a hernia repair and the likelihood of recurrence. Many general surgeons will be uncertain of their own results and recent events suggest that it is unacceptable to guess. An enquiry by the patient about who is to carry out the operation requires a scrupulously honest answer; if it is to be a trainee, this must be stated.

Poor handling of the consent process may lead to complaint and this not infrequently occurs when the task of obtaining consent has been delegated to a trainee who is not fully conversant with the details of the intended procedure, the likely outcome and the risks. Such delegation to the inexperienced is now inappropriate. Consent must be sought by someone who is capable of performing the procedure in question or who has been specifically trained to seek consent for that procedure; ideally it should be obtained by the operating surgeon. In any event the surgeon carrying out the procedure must be involved at some stage in the process of consent, and must have established sufficient rapport with the patient to be reasonably confident that a decision has been reached after considering the available options, which may include a non-surgical course. The Department of Health document[4] rightly indicates that consent to treatment should normally be a process rather than a single event. When a choice of treatment options is offered advice may be sought from more than one healthcare professional, which may be contradictory and lead to confusion. Nevertheless, a full discussion of the benefits, risks and alternatives to the intended procedure is important, not least from a legal perspective since the question is often asked whether the patient would have come to a different decision if better or fuller advice had been available.

If consent to elective surgery is delayed until the day of surgery, a patient may be stressed and vulnerable, and so, for a straightforward procedure, it may be appropriate to introduce the idea at the time of the first consultation. Consent as a process requires discussion on a later occasion. Sadly this is often a hurried affair on the day of surgery, sometimes before the allocation of a bed and without the patient being left alone to read through the small print before being asked to sign a document. Sometimes the doctor or nurse hovers over the patient in the misconception that the signature must be witnessed – sometimes simply waiting to retrieve a pen. These may seem trivial matters, but most people will have experienced the difficulty of signing a binding agreement for something as simple as hiring a car when faced with pages of small print and a queue of impatient customers.

Even when correctly obtained consent has been achieved, problems may still arise during the procedure. Colonoscopy provides a particular example. Consent may have been given freely to this investigation under sedation but, after a period of increasing discomfort, the patient may be heard to say that he or she cannot bear it any more. Abandonment of the investigation would lead to loss of face for both parties and the need for a subsequent barium enema or a repeat of the procedure itself; there is always the knowledge that the patient often forgets the episode. Nevertheless, the operator must be alive to even unspoken tension and the specialist nurse in this situation is properly placed as the patient's advocate.

Finally, it is worthwhile considering the ethical requirement for research in terms of the information given to the patient. This has been of a considerably higher standard than has been exercised for procedures with no research component. The use of carefully edited patient information leaflets and specific consent forms has been a standard requirement by local ethics research committees for some years. The present process of change in our understanding of consent is to some extent a raising of the ethical standards of conventional practice to those required in research. It is worth reflecting on the fact that conventional practice may encompass treatment that is not always standard and is sometimes frankly idiosyncratic. Such treatment would not be allowed within a randomized clinical trial without rigorous consideration by an ethics committee. When there is any doubt about the ethics or the legality of an intended procedure a second opinion is in the best interests of both the patient and the surgeon[2].

References

1 Maugham PJ. Medical negligence and the law. *Br J Surg* 2001; **88:** 899–900.

2 Senate of Surgery of Great Britain and Ireland. *The Surgeon's Duty of Care.* London: Senate of Surgery of Great Britain and Ireland, 1997.

3 General Medical Council. *Seeking Patients' Consent: The Ethical Considerations.* London: General Medical Council, 1998.

4 Department of Health. *Reference Guide to Consent for Examination or Treatment.* London: Department of Health, 2001.

5 Consent Working Party. *Report of the Consent Working Party: Incorporating Consent Toolkit.* London: British Medical Association, 2001.

6 Panting G. *Consent to Treatment.* London: Medical Protection Society, 1999.

7 Gilberthorpe J. *Consent to Treatment.* London: Medical Defence Union, 1999.

8 Branthwaite M. *Law for Doctors: Principles and Practicalities.* London: Royal Society of Medicine Press, 2000.

9 *Sidaway – v – Board of Governors of the Bethlem Royal Hospital* (1985) AC 871.

10 *Canterbury – v – Spence* (1972) 464 F 2a 7772.

Systematic review

Systematic review of randomized clinical trials of surgical treatment for carpal tunnel syndrome

A. A. M. Gerritsen, B. M. J. Uitdehaag[*], D. van Geldere[†], R. J. P. M. Scholten[‡],
H. C. W. de Vet and L. M. Bouter

Institute for Research in Extramural Medicine and [*]Department of Neurology, VU University Medical Centre, Amsterdam, [†]Department of Surgery, Amstelveen Hospital, Amstelveen and [‡]Dutch Cochrane Centre, Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to: Ms A. A. M. Gerritsen, Institute for Research in Extramural Medicine, VU University Medical Centre, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands (e-mail aam.gerritsen.emgo@med.vu.nl)

Background: Carpal tunnel syndrome (CTS) is a common disorder for which several surgical treatment options are available. However, there is no consensus on the most effective method of treatment. The object of this systematic review is to compare the efficacy of the various surgical techniques in relieving the symptoms of CTS and promoting return to work and/or activities of daily living.

Methods: Computer-aided searches of Medline, EMBASE and the Cochrane Controlled Trials Register were conducted, together with reference checking. A rating system, based on the number of studies and their methodological quality and findings, was used to determine the strength of the available evidence for the efficacy of the treatment.

Results: Fourteen studies were included in the review. None of the alternatives to standard open carpal tunnel release (OCTR) seems to offer better relief of symptoms. There is conflicting evidence about whether endoscopic carpal tunnel release results in earlier return to work and/or activities of daily living.

Conclusion: Standard OCTR is still the preferred method of treatment for CTS. It is just as effective as the alternatives, but is technically less demanding, so incurs a lower risk of complications and of added costs.

Paper accepted 16 May 2001

British Journal of Surgery 2001, 88, 1285–1295

Introduction

Carpal tunnel syndrome (CTS) is caused by compression of the median nerve at the wrist which results in symptoms of pain, paraesthesia and hypoaesthesia in the hand. Conservative and surgical options are available to treat the condition. Surgery consists of dividing the transverse carpal ligament, thereby increasing the tunnel volume[1,2] and reducing the pressure on the nerve[3]. In Denmark, the estimated cumulative incidence of operations for CTS is 0·61 per 1000 per year[4]. Various surgical techniques are available, however, there has been considerable discussion about which method is the most effective.

Until recently, open carpal tunnel release (OCTR) with a long palmar curvilinear incision was the standard procedure[5]. In addition to the transverse carpal ligament, the overlying structures from the skin to the median nerve are divided. Sometimes an epineurotomy is performed, particularly if the nerve sheath (epineurium) is thickened[6]. If there is scar tissue within the nerve, an internal neurolysis may be carried out to separate the involved fascicles from this fibrosis[7]. Endoscopic carpal tunnel release (ECTR) is a relatively new procedure. Its putative advantage is that, by dividing the transverse carpal ligament from within the carpal tunnel, the overlying structures are left intact. This may decrease postoperative morbidity and could potentially hasten return to work. Two techniques are commonly used for ECTR, the single-portal technique described by Agee *et al.*[8,9] and the two-portal technique described by Chow[10,11]. Since the introduction of ECTR various types of new incisions have been introduced for OCTR to try to reduce surgical trauma and hence recovery time[12].

The object of this systematic review is to compare the short- and long-term efficacy of the various surgical treatment options for relieving CTS symptoms and promoting return to work and/or activities of daily living.

Methods

Search and selection of studies

To identify publications, a search was made in Medline (January 1966 to March 2000), EMBASE (January 1988 to February 2000) and the Cochrane Controlled Trials Register (2000, issue 1), together with reference checking. A generic search for randomized clinical trials (RCTs)[13] was combined with a specific search for CTS (using the keywords carpal tunnel syndrome, carpal tunnel, carpal syndrome and tunnel syndrome). To be included, a study had to meet the following criteria: (1) the study population consisted of patients with CTS; (2) different surgical techniques were compared; (3) the study was designed as a RCT; and (4) the results were published as a full report, written in Dutch, English, French or German. Studies were selected by two reviewers (A.A.M.G., R.J.P.M.S.) independently and disagreements were discussed to reach a consensus.

Assessment of methodological quality

Two reviewers (A.A.M.G., B.M.J.U.) independently assessed the methodological quality of the included studies and disagreements were resolved at a consensus meeting. The criteria that were applied have been recommended for systematic reviews in the field of musculoskeletal disorders[14]. This list of criteria was adapted for CTS with regard to prognostic indicators (c) and outcome measures (h) (*Table 1*). Moreover, as the intervention was surgery, the criteria 'care provider blinded' and 'compliance acceptable' were omitted from the original list. The criterion 'patient blinded' was applied only in studies comparing OCTR and OCTR with an additional procedure, because with those techniques similar incisions were made. The list contains criteria referring to internal validity, external validity and statistical considerations. Criteria could be scored as positive ('yes'), negative ('no') or unclear ('don't know'). Studies with a negative score for 'adequate randomization' (b1) were excluded from further analysis. The quality score of the studies was based on the number of positive scores for internal validity.

Table 1 Criteria for the assessment of methodological quality of randomized clinical trials evaluating the efficacy of surgical treatment options for carpal tunnel syndrome*

Patient selection
- a Were the eligibility criteria specified?
- b Treatment allocation:
  - 1 Was a method of randomization applied?
  - 2 Was the treatment allocation concealed?
- c Were the groups similar at baseline with regard to the most important prognostic indicators?

Interventions
- d 1 Was the index intervention described explicitly?
  - 2 Was/were the control intervention(s) described explicitly?
- e Were co-interventions avoided or similar for all groups?
- f Was the patient blinded for the intervention?

Outcome measurement
- g Was the outcome assessor blinded to the intervention?
- h Were the outcome measures relevant?
- i Were complications described?
- j Was the drop-out and loss to follow-up rate described and acceptable?
- k Timing follow-up measurements:
  - 1 Was a short-term follow-up measurement performed?
  - 2 Was a long-term follow-up measurement performed?
- l Was the timing of the outcome assessment similar for all groups?

Statistics
- m Was the sample size described for each group?
- n Did the analysis include an intention-to-treat analysis?
- o Were point estimates and measures of variability presented for the primary outcome measures?

*All criteria were scored yes (+), no (–) or don't know (?). Criteria are related to internal validity (b1, b2, c, e, f, g, j, l, n), external validity (a, d1, d2, h, i, k1, k2) and statistics (m, o). Operation of the criteria is available from the authors on request

Data extraction

Data from the articles were extracted independently by two reviewers (A.A.M.G., D.v.G.) and recorded on a standard form. Information was collected on participants (age, sex, duration of symptoms, clinically and/or electrophysiologically confirmed CTS, number of patients treated bilaterally, number of patients or hands randomized), interventions (surgical technique), outcome measures, timing of follow-up measurements, and results (point estimates and measures of variability, number of patients or hands). Although data on all reported outcomes were extracted, measures on symptoms (e.g. pain, percentage of patients with improved symptoms) were considered as primary outcomes, because these are of the greatest importance to patients[15,16]. Also, time to return to work and/or activities of daily living was considered as the primary outcome measure, because this indicates how quickly the patient recovered. Information on complications was also recorded.

Statistical analysis

The quantitative analysis (meta-analysis) was limited to studies that were clinically homogeneous, i.e. for which the participants, interventions, outcome measures and timing of follow-up measurements were considered to be similar. Study results were combined using a fixed-effects model, or a random-effects model if the studies were statistically

Table 2 Methodological quality of randomized clinical trials evaluating the efficacy of surgical treatment options for carpal tunnel syndrome

		Internal validity										External validity							Statistics		Conclusion†		
Reference	Technique index intervention	b1	b2	c	e	f	g	j	l	n	Quality score*	a	d1	d2	h	i	k1	k2	m	o	Symptoms ≤ 3 months	Symptoms > 3 months	Return to work or ADL
ECTR *versus* OCTR																							
Brown *et al.*[27]	Chow: extrabursal	+	−	+	+		+	+	+	+	7	+	+	+	+	+	+	−	−	+	Neutral		Positive
Benedetti and Sennwald[18], Sennwald and Benedetti[19]	Agee	+	+	+	+		?	+	+	−	6	+	+	+	+	+	+	−	+	+			Positive
Jacobsen and Rahme[28]	Chow: transbursal	?	?	+	+		−	+	+	+	5	+	+	+	+	+	+	+	+	+			Neutral
Erdmann[29]	Chow: extrabursal	+	?	+	?		?	?	+	+	4	+	+	+	+	+	+	+	−	−	Neutral	Neutral	Positive
Hoefnagels *et al.*[30]	Agee	?	?	+	+		?	+	+	−	4	−	+	+	+	+	+	−	+	+	Neutral		Neutral
Stark and Engkvist-Löfmark[31]	Agee	?	?	?	+		?	+	+	+	4	−	+	+	+	+	+	+	+	−			Positive
Foucher *et al.*[32]	Agee	?	?	?	?		?	?	+	?	1	−	+	+	+	+	+	+	−	−			Neutral
OCTR: new *versus* standard incision																							
Nakamichi and Tachibana[33]	Short + US	+	?	?	+		+	+	+	+	6	+	+	+	+	+	+	+	−	+	Neutral	Neutral	
Brüser *et al.*[20], Richter and Brüser[21]	Short incision	+	?	+	−		?	+	+	+	5	+	+	+	+	−	+	−	+	−	Neutral		Neutral
Citron and Bendall[34]	Ulnar L incision	?	?	+	?		?	+	+	+	4	−	+	+	+	+	+	+	+	−		Neutral	
OCTR with or without internal neurolysis																							
Mackinnon *et al.*[35]		+	+	+	+	+	+	+	+	?	8	+	+	+	+	−	−	+	+	+		Neutral	
Lowry and Follender[36]		+	?	?	+	+	+	+	+	−	6	+	+	+	+	+	+	−	+	+	Neutral		
Holmgren *et al.*[22,23]		?	?	?	+	?	?	+	+	+	4	+	+	+	+	−	+	+	−	−	Neutral	Neutral	
Open carpal tunnel release with or without epineurotomy																							
Leinberry *et al.*[37]		+	?	+	+	?	+	+	+	+	7	+	+	+	+	−	−	+	+	−		Neutral	

All criteria were scored yes (+), no (–) or don't know (?). Criterion f (patient blinded) was applied only when similar incisions were used. *Number of internal validity criteria scored positive. †Positive conclusion: index intervention significantly ($P < 0{\cdot}05$) more effective than the control intervention(s) in relieving symptoms of carpal tunnel syndrome (3 months or less and more than 3 months) or promoting return to work and/or activities of daily living (ADL); neutral conclusion: no significant difference between index intervention and control intervention(s); blank: no outcomes on symptoms or return to work and/or activities of daily living, or no short- or long-term follow-up measurement. ECTR, endoscopic carpal tunnel release; OCTR, open carpal tunnel release; US, ultrasonography

heterogeneous. For studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling, a qualitative analysis was performed. In such cases a rating system was used consisting of four levels of evidence based on the number of studies, their methodological quality and their findings[17]: level 1 – strong evidence, provided by generally consistent findings in multiple high-quality RCTs; level 2 – moderate evidence, provided by generally consistent findings in one high-quality RCT and one or more low-quality RCTs, or by generally consistent findings in multiple low-quality RCTs; level 3 – limited or conflicting evidence, with only one RCT (either high or low quality) or inconsistent findings in multiple RCTs respectively; level 4 – no evidence (no RCTs).

Conclusions with regard to the findings of the studies were based on the statistical significance ($P < 0{\cdot}05$) of the results of the outcome measures on symptoms and return to work and/or activities of daily living, as assessed by the reviewers. Both short-term (3 months or less) and long-term (more than 3 months) results for symptom improvement were taken into consideration. The conclusion of a RCT was considered to be positive if the index intervention was significantly more effective than the control intervention(s), neutral if there were no statistically significant differences, and negative if the index intervention was significantly less effective than the control intervention(s). If at least 75 per cent of the studies had a similar score (either positive, neutral or negative), the findings were considered to be consistent. A RCT was (arbitrarily) regarded to be of high quality if at least five of the eight (or nine if patient blinding was included) internal validity criteria were scored as positive. A sensitivity analysis was performed to examine the results when high quality was defined as a positive score of 4 or more, or 6 or more for internal validity. The influence of considering findings to be consistent if at least

67 per cent of the studies had a similar score was also examined.

Results

Search and selection of studies

Twenty-one publications met the inclusion criteria, 20 of which were found in Medline. Searching EMBASE resulted in the identification of one additional publication. Data from two studies were published twice (in German and in English), so the data from both sets of two papers were combined[18–21]. The same was done for a trial in which the short- and long-term results were reported separately[22,23]. Four studies were excluded from further analysis because the patients were not adequately randomized[8,24–26]. Fourteen studies were finally included in the review.

Methodological quality

The two reviewers initially agreed on 90 per cent of the assessments of methodological quality. Disagreement, as a result of reading (65 per cent) and interpretation (35 per cent) errors, was resolved at the consensus meeting. *Table 2* shows the scores. The studies scored positive on one to eight of the eight (or nine) internal validity criteria. Eight of the 14 studies were of high quality. Many studies reported on randomized treatment allocation, but failed to describe the exact procedure (b1) or state whether the method of randomization was concealed (b2). Information on the blinding of the outcome assessor (g) was often not provided. Furthermore, many studies presented the data inadequately (o).

Efficacy of the surgical treatment options

Data from the trials were not pooled statistically because many studies did not present the outcomes in such a way that this pooling was possible (as reflected by the negative scores on criterion o shown in *Table 2*). Furthermore, the studies were clinically heterogeneous with regard to study population (different eligibility criteria), interventions (different surgical techniques), outcome measures (different symptoms measured, different definition of time to return to work) and timing of follow-up measurements. Therefore, all conclusions with regard to the efficacy of the surgical treatment options were based on the strength of the available evidence according to the predefined rating system. The conclusions of the studies with regard to symptoms (short- and long-term follow-up) and return to work and/or activities of daily living are shown in *Table 2*. *Table 3* presents the study characteristics (participants, interventions, results for symptoms and return to work and/or activities of daily living, complications).

Endoscopic *versus* open carpal tunnel release

Three high-quality[18,19,27,28] and four low-quality[29–32] studies were identified. Different types of ECTR were applied, but the results were combined because all the techniques divide the transverse carpal ligament from within the carpal tunnel and differ only in the way in which this is achieved. Three studies evaluated the short-term effects on symptoms (one of high quality[27] and two of low quality[29,30]); all concluded that ECTR was equally effective as OCTR. With regard to the long-term results for symptoms, no differences between the groups were found in one low-quality study[29]. Four studies[18,19,27,29,31] concluded that patients returned to work and/or activities of daily living earlier after ECTR, while the other three studies[28,30,32] found no difference. In summary, there is moderate evidence that in the short term (level 2), and limited evidence that in the long term (level 3), ECTR and OCTR provide similar degrees of symptom relief; there is conflicting evidence (level 3) that ECTR results in earlier return to work and/or activities of daily living.

Open carpal tunnel release: new *versus* standard incision

Two high-quality studies[20,21,33] and one low-quality study[34] were found. Although the three studies used different types of new incision, they were considered to be more or less similar because the purpose of all these new types of incision is to provide an alternative to ECTR, by reducing postoperative morbidity (as with ECTR) while also releasing the transverse carpal ligament (partly) under direct vision (as in OCTR). The two high-quality studies[20,21,33] concluded that there were no differences between the groups with regard to relief of symptoms in the short term (1·5–3 months). Long-term follow-up measurements (0·5–2 years) in one high-quality[33] and one low-quality[34] study also showed no differences between the groups in terms of symptom relief. Only one high-quality study[20,21] examined the time to return to work, but no difference in effect between the two types of incision was found. There is, therefore, strong evidence that in the short term (level 1), and moderate evidence that in the long term (level 2), OCTR with a new type of incision is equally effective in relieving CTS symptoms as OCTR with a standard incision. Furthermore, there is limited evidence (level 3) that time to return to work is similar for both types of incision.

Table 3 Characteristics of randomized clinical trials evaluating the efficacy of surgical treatment options for carpal tunnel syndrome

			Results*			
Reference	Participants	Intervention	Symptoms ≤ 3 months	Symptoms > 3 months	Return to work or ADL	Complications
ECTR *versus* OCTR						
Brown *et al.*[27]	Mean age 56 years, 68% female, mean duration of symptoms 24 months; clinical and electrophysiological CTS; idiopathic CTS; 24 of 145 patients treated bilaterally	(1) ECTR: two-portal extrabursal Chow technique ($n = 84$ hands) (2) OCTR ($n = 85$ hands)	Improvement in symptoms (paraesthesia, numbness) in 99% (1) and 98% (2) after 12 weeks (difference 1% (95% c.i. −3 to 5%))	No data given	Median 14 (1) and 28 (2) days (significant difference between groups)	Significantly more scar tenderness in (2) *versus* (1) after 12 weeks (no significant difference after 3 and 6 weeks). No significant difference between groups in pillar tenderness at 3, 6 and 12 weeks; 1 partial transection of superficial palmar arch, 1 digital nerve contusion, 1 ulnar nerve neurapraxia and 1 wound haematoma in (1)
Benedetti and Sennwald[18], Sennwald and Benedetti[19]	Mean age 53 years, 79% female, mean duration of symptoms 9 months; clinical and electrophysiological CTS; idiopathic CTS	(1) ECTR: one-portal Agee technique ($n = 25$ patients) (2) OCTR ($n = 22$ patients)	No data given	No data given	Mean 24 (1) and 42 (2) days (significant difference between groups)	1 conversion to OCTR and 1 transient neurapraxia in (1); 1 painful hypertrophic scar and 1 reflex sympathetic dystrophy in (2)
Jacobsen and Rahme[28]	Mean age 46 years, 72% female; clinical and electrophysiological CTS; idiopathic CTS; 3 of 29 patients treated bilaterally	(1) ECTR: two-portal transbursal Chow technique ($n = 16$ hands) (2) OCTR ($n = 16$ hands)	No data given	No data given	Mean 17 (1) and 19 (2) days (no significant difference between groups)	3 transient numbness on radial side of ring finger in (1); 1 prolonged wound secretion in (2)
Erdmann[29]	Mean age 53 years, 73% female, mean duration of symptoms 24 months; clinical and electrophysiological CTS; not only idiopathic CTS; 34 of 71 patients treated bilaterally (25 patients 1 hand ECTR, 1 hand OCTR simultaneously)	(1) ECTR: two-portal extrabursal Chow technique ($n = 53$ hands) (2) OCTR ($n = 52$ hands)	Significantly more improvement in pain in (1) *versus* (2) after 1, 2 and 4 weeks, but no significant difference between groups after 3 months	No significant difference in pain between groups after 6 and 12 months	Mean 14 (1) and 39 (2) days (only patients not having simultaneous operation on both hands) (significant difference between groups)	1 ulnar nerve paraesthesia and 1 incomplete release in (1); 1 wound infection, 1 scar tethering and 5 scar hypertrophy in (2)

Table 3 (continued)

			Results*			
Reference	Participants	Intervention	Symptoms ⩽3 months	Symptoms >3 months	Return to work or ADL	Complications
Hoefnagels *et al.*[30]	Mean age 51 years, 74% female, mean duration of symptoms 21 months; clinical and electrophysiological CTS	(1) ECTR: one-portal Agee technique (*n* = 87 patients) (2) OCTR (*n* = 91 patients)	76% free of tingling in both groups after 1 week, and no significant difference in symptom severity score between groups after 3 months	No data given	More than 4 weeks' absence from work in 16% (1) and 13% (2) (difference 3% (95% c.i. −7 to 14%))	Significantly less postoperative pain in (1) *versus* (2) after 1 week; 1 conversion to OCTR, 1 broken knife left in operation wound and 1 increased numbness in fingertips in (1)
Stark and Engkvist-Löfmark[31]	Mean age 53 years, 55% female, mean duration of symptoms 29 months; 15 patients clinical and electrophysiological CTS, 5 patients only clinical CTS; idiopathic CTS; all patients (*n* = 20) treated bilaterally	(1) ECTR: one-portal Agee technique (*n* = 20 hands) (2) OCTR (*n* = 20 hands)	No data given	No data given	Mean 20 (1) *versus* 30 (2) days (significant difference between groups)	1 subcutaneous haematoma and 1 loss of strength and mobility in the wrist in (1); 2 loss of strength and 1 swollen/stiff fingers in (2)
Foucher *et al.*[32]	Only clinical CTS; 2 of 249 patients treated bilaterally	(1) ECTR: one-portal Agee technique (*n* = 54 hands) (2) OCTR (*n* = 69 hands) (3) OCTR with anterior ligamentoplasty type I (*n* = 59 hands) (4) OCTR with anterior ligamentoplasty type II (*n* = 69 hands)	No data given	No data given	No significant difference in time to return to work between groups (all 17 days)	1 algodystrophy and 2 conversions to OCTR in (1)
OCTR: new *versus* standard incision						
Nakamichi and Tachibana[33]	Mean age 58 years, 100% female; clinical and electrophysiological CTS; idiopathic CTS	(1) OCTR with short incision (1·0–1·5 cm) with ultrasonographic assistance (*n* = 50 patients) (2) OCTR (*n* = 53 patients)	No significant difference in symptoms (numbness and paraesthesia) between groups after 3, 6, 13 weeks	No significant difference in symptoms (numbness and paraesthesia) between groups after 6, 12, 24 months; 86% (1) and 89% (2) free of symptoms after 24 months (difference −3% (95% c.i. −16 to 10%))	No data given	Significantly more scar pain and tenderness in (2) *versus* (1) after 3, 6, 13 weeks; no other complications
Brüser *et al.*[20], Richter and Brüser[21]	Mean age 54 years, 78% female, mean duration of symptoms 41 months; clinical and electrophysiological CTS; idiopathic CTS	(1) OCTR with short incision (2·5 cm) (*n* = 38 patients) (2) OCTR with long incision (4·5 cm) (sometimes with epineurotomy) (*n* = 42 patients)	No significant difference in night symptoms, tingling and numbness between groups after 1, 2, 3, 6 weeks	No data given	Median 21 (mean 17·6) *versus* 18 (18·8) days (no significant difference between groups)	No significant difference in scar tenderness and tenderness of radial and ulnar pillars after 1, 2, 3, 6 weeks

Table 3 (continued)

			Results*			
Reference	Participants	Intervention	Symptoms ≤ 3 months	Symptoms > 3 months	Return to work or ADL	Complications
Citron and Bendall[34]	Mean age 52 years, 83% female; only clinical CTS; not only idiopathic CTS	(1) OCTR with ulnar L incision ($n = 23$ patients) (2) OCTR with standard incision ($n = 27$ patients)	No data given	95% (1) and 88% (2) free of symptoms after 12 months (difference 7% (95% c.i. −9 to 22%))	No data given	No significant difference in pillar pain between groups. Significantly more recovery in scar sensitivity in (1) *versus* (2); 1 delayed wound healing in each group
OCTR with or without internal neurolysis						
Mackinnon *et al.*[35]	Mean age 59 years, 81% female; clinical CTS only; idiopathic CTS; 4 of 59 patients treated bilaterally	(1) OCTR with internal neurolysis ($n = 29$ patients/31 hands available for evaluation) (2) OCTR ($n = 30$ patients/32 hands)	No data given	Improvement in symptoms in 81% (1) and 88% (2) after 12 months (difference −7% (95% c.i. −25 to 11%))	No data given	No data given
Lowry and Follender[36]	Clinical and electrophysiological CTS; severe CTS; 9 of 41 patients treated bilaterally	(1) OCTR with internal neurolysis ($n = 25$ hands) (2) OCTR ($n = 25$ hands)	Excellent or good clinical response (pain, sensory deficit, complications) according to neurologist in 67% (1) and 65% (2) after 3 months (difference 2% (95% c.i. −26 to 29%))	No data given	No data given	4 persistent incisional pain, 1 hand swelling and 1 adhesive capsulitis in (1); 3 persistent incisional pain and 1 causalgia in (2)
Holmgren *et al.*[22,23]	Mean age 50 years, 69% female; clinical and electrophysiological CTS	(1) OCTR with internal neurolysis ($n = 24$ patients?) (2) OCTR ($n = 24$ patients?)	No significant difference in pain, paraesthesia and hypoaesthesia between groups after 3–4 weeks	89% free of symptoms in both groups after 6 months and 86% (1) *versus* 75% (2) after 3–4 years (difference 11% (95% c.i. −15 to 36%))	No data given	No complications ascribable to internal neurolysis
OCTR with or without epineurotomy						
Leinberry *et al.*[37]	Mean age 65 years, 59% female, mean duration of symptoms 32 months; clinical and electrophysiological CTS; not only idiopathic CTS; 6 of 44 patients treated bilaterally	(1) OCTR with epineurotomy ($n = 25$ hands) (2) OCTR ($n = 25$ hands)	No data given	56% (1) and 60% (2) free of symptoms (pain, altered sensibility, paraesthesia, loss of manual dexterity) after 1 year (difference −4% (95% c.i. −31 to 23%))	No data given	No data given

ADL, activities of daily living; c.i., confidence interval; CTS, carpal tunnel syndrome; ECTR, endoscopic carpal tunnel release; OCTR, open carpal tunnel release. *$P < 0.05$ was considered significant

Open carpal tunnel release with or without internal neurolysis

Two high-quality studies[35,36] and one low-quality study[22,23] were included. One of the high-quality studies[36] examined the clinical response 3 months after operation and found no significant difference between the groups. The low-quality study[22,23] also found no difference in improvement of symptoms between the groups in the short term (3–4 weeks). One high-quality[35] and one low-quality[22,23] study also found equal relief from symptoms in both groups in the long term (6 months and 4 years, respectively). There is, therefore, moderate evidence (level 2) that division of the transverse carpal ligament with internal neurolysis does not improve short- or long-term symptom relief.

Open carpal tunnel release with or without epineurotomy

Only one high-quality study[37] was identified. The follow-up measurement after 1 year revealed no significant difference in improvement of symptoms between the groups, indicating limited evidence (level 3) that adjuvant epineurotomy offers no additional benefit in long-term symptom relief compared with OCTR alone.

Sensitivity analysis

Changing the cut-off point of the quality score to four or more, and to six or more positive criteria, resulted in 13 and six high-quality studies respectively (*Table 2*). If high quality is defined as at least six positive criteria, the level of evidence for ECTR resulting in earlier return to work and/or activities of daily living compared with OCTR will rise from conflicting evidence (level 3) to strong evidence (level 1). When consistent findings are defined as 67 per cent of the studies reporting the same conclusion instead of 75 per cent, the level of evidence for ECTR resulting in earlier return to work and/or activities of daily living compared with OCTR also rises from conflicting evidence (level 3) to strong evidence (level 1).

Complications

All studies comparing ECTR with OCTR reported complications. It seems that ECTR gives more transient nerve problems (e.g. neurapraxia, numbness, paraesthesia) and OCTR more wound problems (e.g. infection, hypertrophic scar, scar tenderness). In a few cases ECTR had to be abandoned and OCTR was performed instead. There seems to be no difference in pillar pain between OCTR with a new or a standard incision; however, in two studies[33,34] more scar pain and tenderness was found with the standard incision, although in the third study[20,21] this was not confirmed. No conclusions can be drawn with regard to differences in complications between OCTR and OCTR with an additional procedure (internal neurolysis or epineurotomy). This is due to the fact that only one study reported complications[36], one merely stated that there were no complications ascribable to internal neurolysis[22,23] and the two other studies provided no information on complications[35,37].

Discussion

Search and selection of studies

The search was restricted to Medline, EMBASE, the Cochrane Controlled Trials Register and trials published as a full paper, written in Dutch, English, French or German. Therefore, some studies might have been missed, which may have led to bias. Unpublished studies and studies that were presented only in abstract form are more likely to have non-significant results[38,39]. Furthermore, trials with significant results are more likely to be published in English[40].

Methodological quality

There is no consensus on which criteria should be used to assess the methodological quality of RCTs. However, criteria that are regarded as being most important in reducing bias, concealment of allocation and double blinding are included in the list used for this review[41]. The other criteria in the list are generally accepted methodological criteria that are also included in most of the other available lists[42]. In fact, the focus was on the quality of the reporting. It is possible that a trial did meet a particular criterion, but that for the sake of conciseness this aspect was not described in detail in the publication. One drawback of combining information on different study characteristics into a sum-score for methodological quality is that a positive score on one criterion may compensate for a negative score on another. Therefore a sum-score could conceal methodological shortcomings and variation in methods between studies[43].

Efficacy analysis

Owing to relatively small study populations (half of the studies had 20 to 30 patients in each group) clinically relevant differences in outcomes between treatment options could remain undetected. Statistical pooling would have increased the power, but it was decided not to pool the data and to perform a qualitative analysis, based on levels of evidence, instead. It is therefore possible that some smaller differences between treatment groups may have been missed. These were not statistically significant in the individual trials, but would have become statistically significant if the data had been pooled. Still, this does not seem likely on reviewing the data from the trials, because the differences that were not statistically significant were mostly so small that they were also not clinically relevant.

The strength of the evidence for the efficacy of an intervention is based partly on the methodological quality of the studies. The difference between high- and low-quality studies in this review was based on an arbitrarily chosen cut-off point, and varying this point leads to a different conclusion with regard to the efficacy, as was noted for ECTR resulting in earlier return to work and/or activities of daily living compared with OCTR. No consensus has yet been reached on how to assess the strength of the available evidence and so the levels of evidence used in this review are, to some extent, arbitrary. It was decided to apply this rating system because it has good face validity, is simple and explicit, and has already been applied in several reviews on the effectiveness of various treatment options for low back pain[17,44].

None of the alternatives to standard OCTR (i.e. ECTR, OCTR with a new type of incision, and OCTR with internal neurolysis or epineurotomy) seems to offer better relief from CTS symptoms in the short or long term. There is conflicting evidence for ECTR resulting in earlier return to work and/or activities of daily living than OCTR, but the evidence becomes strong when the assumptions for the rating system are changed slightly.

The American Academy of Neurology recommends OCTR for the surgical treatment of CTS, a guideline based on so-called 'moderate clinical certainty'[45]. On the basis of the results of the present review, OCTR would also be recommended because the alternatives do not provide better relief from symptoms. The only possible advantages of ECTR would be fewer wound problems and earlier return to work and/or activities of daily living. Possible disadvantages are higher complication rates (nerve problems) and costs. Overall complication rates seem to be similar for OCTR and ECTR when reviewing the published studies[46]. However, it should be noted that, although the complication rates may be similar, many difficult cases are immediately excluded from ECTR, for example patients needing an adjuvant procedure (e.g. synovectomy in the case of inflammatory arthritis) and patients with space-occupying lesions or with stiff (arthritic) wrists[29,47]. A cost-effectiveness study concluded that the two techniques have similar total costs, but that ECTR is more costly if the difference between the techniques in mean time to return to work is less than 21 days[48]. Of the four studies included in this review that found a difference in time to return to work[18,19,27,29,31], only one reported a difference of more than 21 days[29].

Conclusion

Standard OCTR is still the preferred method of treatment for CTS because, while it is just as effective as the alternatives, it is technically less demanding and so incurs a lower risk of complications and added costs.

Acknowledgements

Financial support was provided by the Health Care Insurance Council of the Netherlands.

References

1 Ablove RH, Peimer CA, Diao E, Oliverio R, Kuhn JP. Morphologic changes following endoscopic and two-portal subcutaneous carpal tunnel release. *J Hand Surg [Am]* 1994; **19A**: 821–6.

2 Richman JA, Gelberman RH, Rydevik BL, Hajek PC, Braun RM, Gylys-Morin VM *et al.* Carpal tunnel syndrome: morphologic changes after release of the transverse carpal ligament. *J Hand Surg [Am]* 1989, **14A**: 852–7.

3 Okutsu I, Ninomiya S, Hamanaka I, Kuroshima N, Inanami H. Measurement of pressure in the carpal canal before and after endoscopic management of carpal tunnel syndrome. *J Bone Joint Surg [Am]* 1989; **71A**: 679–83.

4 Ebskov LB, Boeckstyns MEH, Sørensen AI. Operative treatment of carpal tunnel syndrome in Denmark. Results of a questionnaire. *J Hand Surg [Br]* 1997; **22B**: 761–3.

5 Taleisnik J. The palmar cutaneous branch of the median nerve and the approach to the carpal tunnel. An anatomical study. *J Bone Joint Surg [Am]* 1973; **55A**: 1212–17.

6 Fissette J, Onkelinx A. Treatment of carpal tunnel syndrome. Comparative study with and without epineurolysis. *Hand* 1979; **11**: 206–10.

7 Curtis RM, Eversmann WW Jr. Internal neurolysis as an adjunct to the treatment of the carpal-tunnel syndrome. *J Bone Joint Surg [Am]* 1973; **55A**: 733–40.

8 Agee JM, McCarroll HR Jr, Tortosa RD, Berry DA, Szabo RM, Peimer CA. Endoscopic release of the carpal tunnel: a randomized prospective multicenter study. *J Hand Surg [Am]* 1992; **17A**: 987–95.

9 Agee JM, McCarroll HR, North ER. Endoscopic carpal tunnel release using the single proximal incision technique. *Hand Clin* 1994; **10**: 647–59.

10 Chow JCY. Endoscopic release of the carpal ligament: a new technique for carpal tunnel syndrome. *Arthroscopy* 1989; **5**: 19–24.

11 Chow JCY. The Chow technique of endoscopic release of the

carpal ligament for carpal tunnel syndrome: four years of clinical results. *Arthroscopy* 1993; **9:** 301–14.
12 Bromley GS. Minimal-incision open carpal tunnel decompression. *J Hand Surg [Am]* 1994; **19A:** 119–20.
13 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309:** 1286–91.
14 van Tulder MW, Assendelft WJJ, Koes BW, Bouter LM. Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine* 1997; 22: 2323–30.
15 Katz JN, Gelberman RH, Wright EA, Lew RA, Liang MH. Responsiveness of self-reported and objective measures of disease severity in carpal tunnel syndrome. *Med Care* 1994; **32:** 1127–33.
16 Glowacki KA, Breen CJ, Sachar K, Weiss AP. Electrodiagnostic testing and carpal tunnel release outcome. *J Hand Surg [Am]* 1996; **21A:** 117–21.
17 van Tulder MW, Esmail R, Bombardier C, Koes BW. Back schools for non-specific low back pain (Cochrane Review). In: *The Cochrane Library, Issue 4.* Oxford: Update Software, 2000.
18 Benedetti VR, Sennwald G. Endoskopische Dekompression des N. medianus nach Agee: Prospektive Studie mit Vergleich zur offenen Dekompression. *Handchir Mikrochir Plast Chir* 1996; **28:** 151–5.
19 Sennwald GR, Benedetti R. The value of one-portal endoscopic carpal tunnel release: a prospective randomized study. *Knee Surg Sports Traumatol Arthrosc* 1995; **3:** 113–16.
20 Brüser P, Richter M, Larkin G, Lefering R. The operative treatment of carpal tunnel syndrome and its relevance to endoscopic release. *Eur J Plast Surg* 1999; **22:** 80–4.
21 Richter VM, Brüser P. Die operative Behandlung des Karpaltunnelsyndroms: ein Vergleich zwischen langer und kurzer Schnittfürung sowie endoskopischer Spaltung. *Handchir Mikrochir Plast Chir* 1996; **28:** 160–6.
22 Holmgren-Larsson H, Leszniewski W, Linden U, Rabow L, Thorling J. Internal neurolysis or ligament division only in carpal tunnel syndrome – results of a randomized study. *Acta Neurochir* 1985; **74:** 118–21.
23 Holmgren H, Rabow L. Internal neurolysis or ligament division only in carpal tunnel syndrome. II: A 3 year follow-up with an evaluation of various neurophysiological parameters for diagnosis. *Acta Neurochir* 1987; **87:** 44–7.
24 Dumontier C, Sokolow C, Leclercq C, Chauvin P. Early results of conventional *versus* two-portal endoscopic carpal tunnel release. A prospective study. *J Hand Surg [Br]* 1995; **20B:** 658–62.
25 Foulkes GD, Atkinson RE, Beuchel C, Doyle JR, Singer DI. Outcome following epineurotomy in carpal tunnel syndrome: a prospective, randomized clinical trial. *J Hand Surg [Am]* 1994; **19A:** 539–47.
26 Schäfer W, Sander KE, Walter A, Weitbrecht WU. Endoskopische Operation des Karpaltunnelsyndroms nach Agee im Vergleich mit der offenen Operationstechnik. *Handchir Mikrochir Plast Chir* 1996; **28:** 143–6.
27 Brown RA, Gelberman RH, Seiler JG III, Abrahamsson SO, Weiland AJ, Urbaniak JR *et al.* Carpal tunnel release. A prospective, randomized assessment of open and endoscopic methods. *J Bone Joint Surg [Am]* 1993; **75A:** 1265–75.
28 Jacobsen MB, Rahme H. A prospective, randomized study with an independent observer comparing open carpal tunnel release with endoscopic carpal tunnel release. *J Hand Surg [Br]* 1996; **21B:** 202–4.
29 Erdmann MWH. Endoscopic carpal tunnel decompression. *J Hand Surg [Br]* 1994; **19B:** 5–13.
30 Hoefnagels WAJ, van Kleef JGF, Mastenbroek GGA, de Blok JA, Breukelman AJ, de Krom MCTFM. Operatieve behandeling wegens carpaletunnelsyndroom: endoscopisch of klassiek (open)? Een prospectief gerandomiseerd onderzoek. *Ned Tijdschr Geneeskd* 1997; **141:** 878–82.
31 Stark B, Engkvist-Löfmark C. Endoskopische Operation oder konventionelle offene Operationstechnik bei Karpaltunnelsyndrom: eine prospektive, vergleichende Studie. *Handchir Mikrochir Plast Chir* 1996; **28:** 128–32.
32 Foucher G, Buch N, Van Overstraeten L, Gautherie M, Jesel M. Le canal carpien. Peut-il être encore sujet de controverse? *Chirurgie* 1993–94; **119:** 80–4.
33 Nakamichi K, Tachibana S. Ultrasonographically assisted carpal tunnel release. *J Hand Surg [Am]* 1997; **22A:** 853–62.
34 Citron ND, Bendall SP. Local symptoms after carpal tunnel release. A randomized prospective trial of two incisions. *J Hand Surg [Br]* 1997; **22B:** 317–21.
35 Mackinnon SE, McCabe S, Murray JF, Szalai JP, Kelly L, Novak C *et al.* Internal neurolysis fails to improve the results of primary carpal tunnel decompression. *J Hand Surg [Am]* 1991; **16A:** 211–18.
36 Lowry WE Jr, Follender AB. Interfascicular neurolysis in the severe carpal tunnel syndrome. A prospective, randomized, double-blind, controlled study. *Clin Orthop* 1988; **227:** 251–4.
37 Leinberry CF, Hammond NL III, Siegfried JW. The role of epineurotomy in the operative treatment of carpal tunnel syndrome. *J Bone Joint Surg [Am]* 1997; **79A:** 555–7.
38 Egger M, Davey Smith G. Bias in location and selection of studies. *BMJ* 1998; **316:** 61–6.
39 Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. *JAMA* 1994; **272:** 158–62.
40 Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997; **350:** 326–9.
41 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273:** 408–12.
42 Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Controlled Clin Trials* 1995; **16:** 62–73.
43 Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999; **282:** 1054–60.
44 van Tulder MW, Scholten RJPM, Koes BW, Deyo RA. Non-

steroidal anti-inflammatory drugs for low back pain (Cochrane Review). In: *The Cochrane Library, Issue 4*. Oxford: Update Software, 2000.

45 American Academy of Neurology. Practice parameter for carpal tunnel syndrome (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1993; **43:** 2406–9.

46 Boeckstyns MEH, Sørensen AI. Does endoscopic carpal tunnel release have a higher rate of complications than open carpal tunnel release? An analysis of published series. *J Hand Surg [Br]* 1999; **24B:** 9–15.

47 Einhorn N, Leddy JP. Pitfalls of endoscopic carpal tunnel release. *Orthop Clin North Am* 1996; **27:** 373–80.

48 Vasen AP, Kuntz KM, Simmons BP, Katz JN. Open *versus* endoscopic carpal tunnel release: a decision analysis. *J Hand Surg [Am]* 1999; **24A:** 1109–17.

Calcutta University College of Medicine C.U.
LIBRARY

Review

Effect of laparoscopy on immune function

A. Gupta and D. I. Watson

University of Adelaide Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia
Correspondence to: Associate Professor D. I. Watson (e-mail: david.watson@adelaide.edu.au)

Background: Laparoscopic surgery is believed to lessen surgical trauma and so cause less disturbance of immune function. This may contribute to the rapid recovery noted after many laparoscopic operations. Preservation of both systemic and intraperitoneal immunity is particularly important in surgery for sepsis or cancer and so an understanding of the impact of laparoscopy on immune function is relevant.
Methods: Literature on immunological changes following laparoscopy and open surgery was identified from Medline, along with cross-referencing from the reference lists of major articles on the subject.
Results and discussion: Despite a few contradictory reports, systemic immunity appears to be better preserved after laparoscopic surgery than after open surgery. However, the local intraperitoneal immune system behaves in a particular way when exposed to carbon dioxide pneumoperitoneum; suppression of intraperitoneal cell-mediated immunity has been demonstrated in a number of studies. This feature may be clinically important and should be acknowledged when considering laparoscopic surgery in patients with malignancy or sepsis.

Paper accepted 16 May 2001

British Journal of Surgery 2001, **88**, 1296–1306

Introduction

Over the past decade laparoscopic surgery has become integral to general surgical practice, with the advantages over open operation of less postoperative pain, earlier return to normal activity and better cosmetic outcomes demonstrated for a range of procedures. Furthermore, it seems likely that surgery is associated with significant suppression of postoperative immune function; the degree to which this occurs and its duration are determined by the magnitude of the initial surgical insult[1–3]. Because laparoscopic surgery reduces the magnitude of surgical trauma, it may be associated with less systemic immune impairment[4–29]. While many studies have demonstrated a more favourable systemic immune response following laparoscopic surgery, the local immune system within the peritoneal cavity might act differently. It is possible that intraperitoneal immune responses are modulated by factors such as the type of insufflation gas used to maintain the pneumoperitoneum, mechanical factors associated with abdominal wall distension, decreased temperature, increased gas pressure and desiccation due to the drying effect of the insufflation gas. These factors are independent of the magnitude of the surgical trauma.

Understanding this issue is important, as a clear determination of whether laparoscopy is or is not associated with significant immunological advantages has implications for the performance of both oncological resections and laparoscopy in the presence of sepsis.

Systemic immune function

Laparoscopic surgery causes less tissue trauma than open operation and so is likely to be associated with better preservation of systemic immune function. While the improved early clinical outcome following various laparoscopic procedures has usually been attributed to a reduction in postoperative pain, facilitating a quicker recovery, shorter hospital stay and earlier return to physical activity. Though the exact cause for this better clinical outcome is still being investigated, better preservation of systemic immune function might also contribute to this improved recovery[2,30,31]. Following conventional open surgery, immunological function in general is depressed, with adverse alterations in cytokine levels and changes in the function of cellular components of the systemic immune response[1–4,11,13,32–35].

The usual physiological reaction to injury, surgical or non-surgical, is an early rise in serum stress hormone levels together with a decrease in cellular immune response. The latter manifests as a reduction in lymphocyte and macrophage interaction, decreased activity of natural killer (NK) cells, decreased lymphocyte and neutrophil chemotaxis, and a reduction in delayed-type hypersensitivity (DTH) responses[36,37]. Therefore, the overall immune response to surgery in general is reflected mainly in terms of alteration in cytokine functions and the cellular messenger system.

Acute-phase response and cytokines

The acute-phase response (APR) and cytokines are important and necessary components of immunological function. Although cytokine levels do not indicate immune status directly, they are a good guide in the assessment of the activation of the systemic immune system. However, the overproduction of cytokines, or their production at non-inflammatory sites, may lead to deleterious effects on tissues and so a decreased production of cytokines (reduced inflammatory reaction) might be considered beneficial during the postoperative period.

C-reactive protein (CRP) is the most extensively studied APR protein following trauma and surgery; it is a dependable marker for APR. CRP levels usually rise approximately 4–12 h after operation and peak at 24–72 h, thereafter remaining raised for about 2 weeks[33]. Similar changes do not occur in the levels of other APR proteins, such as fibrinogen and transferrin[38–40]. Postoperative CRP levels are significantly lower during the first 2 days after laparoscopic surgery than after open operation[4,6–9,11,12,41–43]. Fornara *et al.*[13] reported significantly lower serum levels of CRP during and after laparoscopic procedures. They also found a less marked increase in interleukin (IL) 6 levels during laparoscopy, extracorporeal shockwave lithotripsy and minor operative procedures than during open procedures. The levels of IL-10 were not influenced by the operative technique used[13]. Similarly, in a prospective randomized study of laparoscopic *versus* small-incision open cholecystectomy, Squirrell *et al.*[10] also demonstrated significantly lower CRP levels following laparoscopic cholecystectomy. However, they found no differences in respiratory function or serum cortisol levels between the two operative groups and concluded that the neuroendocrine component of the metabolic response (cortisol) was not influenced by the type of surgical access. On the other hand, in another clinical study of laparoscopic *versus* minilaparotomy cholecystectomy, McMahon *et al.*[40] found no differences in the levels of CRP or other APR proteins (albumin and transferrin) between the different surgical approaches. Because the open variant was performed through a much smaller incision than would normally be used for open surgical procedures, these results are consistent with the hypothesis that the trauma of abdominal access influences immunological function. Other studies of laparoscopic *versus* small-incision cholecystectomy also support these findings[38,39].

The cytokines IL-1, tumour necrosis factor (TNF) and IL-6 also play a major role in the APR[2,44]. IL-1 and TNF both act through their soluble receptors[45], and the receptor production is stimulated by the same response that leads to the formation of these cytokines. These receptors are believed to regulate cytokine activity[45] and the serum levels of these soluble receptors reflect serum cytokine levels. While no difference in soluble TNF receptor levels has been noted after laparoscopic and conventional surgery[11,34], serum IL-1 receptor levels are significantly lower after the former; this may reflect less inflammation[34].

The expression of IL-6 is believed to be directly proportional to the extent of surgical trauma[46]. Plasma levels correlate well with the invasiveness of the surgical operation and a significant difference has been found in postoperative plasma levels after open and laparoscopic cholecystectomy[6–8,34,41–43,47]. Schwenk *et al.*[48], in a randomized controlled trial of laparoscopic *versus* conventional colorectal resection, also demonstrated a postoperative increase in IL-6 and CRP levels in both study groups, with a more marked response following conventional surgery. However, they did not observe any difference between the peak and overall IL-1 receptor agonist levels in both the groups. Leung *et al.*[14] randomized 34 patients to either laparoscopically assisted or open resection of rectosigmoid carcinoma and found no increase in TNF-α levels in either group. However, serum levels of both IL-1β and IL-6 peaked 2 h after operation, with a significantly smaller response after laparoscopic surgery. The CRP concentration peaked at 48 h and the difference between the two operative groups was statistically significant.

However, other authors have found no consistency in serum IL-6 levels following different surgical approaches. Johnson *et al.*[49] demonstrated significantly higher serum IL-6 levels after laparoscopically assisted colectomy in dogs, compared with the conventional open approach. Stage *et al.*[50] found the same results in a prospective randomized clinical trial. However, Hill *et al.*[51] failed to find any differences in the postoperative IL-6 level following laparoscopic and conventional inguinal hernia repair. This discrepancy could be because the surgical insult caused by open hernia repair is not sufficient to generate increased levels of these markers. In a similar study, no difference in plasma cortisol, growth hormone, prolactin and serum IL-6 levels was found when metabolic and inflammatory responses were compared following laparoscopic and open surgery for inguinal hernia[52]. However, a rise in CRP concentration and suppression of endotoxin-induced TNF-α production was recorded in both of these groups and these changes were greater following open hernia repair[52]. Plasma levels of IL-8, an important chemokine for neutrophils, have also been found to be higher after open surgery than after laparoscopic surgery[34]. Similar results have not been observed by other investigators[41].

Kuntz *et al.*[15] compared laparoscopically assisted and open colonic resection in a rat model and measured the serum levels of cortisone, neopterin and IL-1β during, just before and after operation, and on the first and seventh postoperative days. Significant differences were found between the two study groups for all three variables on the first postoperative day. After a week the levels of cortisone and neopterin had normalized. In addition, bodyweight on day 7 after operation was significantly lower after open surgery in the rat model; this may be due to differences in the anabolic state following laparoscopic compared with open operation.

Kishi *et al.*[16] compared laparoscopically assisted surgery for Crohn's disease with conventional surgery, and found that CRP levels and body temperature were lower following laparoscopic surgery. Furthermore, leucocyte counts after laparoscopic operation were lower than after open surgery. Hildebrandt *et al.*[53] also evaluated markers of surgical trauma following open and laparoscopically assisted resection for Crohn's disease and found increased levels of systemic proinflammatory cytokines (IL-6, IL-10), but without any significant demonstrable difference between the two groups. In this study, CRP also rose after operation, peaking on the second postoperative day; again there was no significant difference between the study groups. However, the authors found a significantly lower plasma granulocyte elastase level after laparoscopic surgery compared with the open operation. Interestingly, Crohn's disease is in general associated with increased levels of T helper (Th) type 1 cytokines (e.g. interferon (IFN) γ, TNF-α, IL-2)[54] and, although the cytokine pattern is less clear, ulcerative colitis appears to be associated with increased levels of IL-5 and IL-10[54,55]. These cytokine changes, which are associated specifically with inflammatory bowel disease, need to be kept in mind when interpreting the results of studies on immunological changes after operation if patients with inflammatory bowel disease are included.

Overall, the outcomes of both experimental and clinical studies clearly demonstrate reduced activation of cytokines IL-1, IL-6 and CRP following laparoscopic surgery compared with equivalent open procedures. However, differences in the activation of other cytokines (e.g. TNF, IL-8) and changes in the levels of acute-phase proteins (fibrinogen, albumin and transferrin) are less clear. As the majority of the clinical studies have been performed using laparoscopic cholecystectomy as the model, caution should be exercised if extrapolating these conclusions to other surgical procedures, especially as the data available for laparoscopic colectomy and inguinal hernia repair have been inconsistent in terms of demonstrating immunological advantages for laparoscopic procedures.

Peripheral leucocyte population and function

Polymorphonuclear (PMN) leucocytes play a key role in the host defence against invading micro-organisms. Surgical stress affects PMN function during the postoperative period. The phagocytic and chemotactic activity of neutrophilic granulocytes, which play a key role in host defence, are reduced after both surgery and trauma[4,35,56]. This impaired phagocytosis is possibly due to serum factors rather than an intrinsic neutrophilic defect[57]. Several studies have evaluated the total leucocyte count and specific leucocyte populations and subpopulations following laparoscopic and open surgery, and have demonstrated a significant increase in overall peripheral leucocyte numbers following open, but not laparoscopic, procedures[4,42,43]. A transient increase in the number of granulocytes has been observed after open operation, but not after laparoscopic surgery[58]. Sietses *et al.*[17] did not observe any difference in systemic white cell count between patients undergoing laparoscopic and those having open Nissen fundoplication. However, they found a significant reduction in the phagocytic activity of PMN cells after open surgery which was not noted following laparoscopic fundoplication.

A significant difference in stimulated oxygen radical production has also been noted between open and laparoscopic techniques[17,35], suggesting a higher state of PMN activation after the former. Similarly, the concentration of elastase, an indicator of neutrophil activation, increases following both open and laparoscopic surgery, but returns to preoperative levels within 3 days after laparoscopic but not open surgery[59]. The CD11b receptor, a β_2-integrin, plays an important role in the migration of PMN cells to the site of infection[60]. Sietses *et al.*[17] found significantly greater surface expression of CD11b in patients undergoing open surgery compared with those having laparoscopic surgery. The postoperative production of hypochloric acid, a potent neutrophil antimicrobial antioxidant, may also be used to assess this cellular activation[61]. Its production has been shown to fall significantly 1 day after open operation, but not after laparoscopic surgery[61].

The peripheral histamine response produced by mast cells exerts a variety of well recognized systemic effects (e.g. allergic, cardiovascular, pulmonary and inflammatory responses). Histamine also alters the function of granulocytes, macrophages and T lymphocytes. Nies *et al.*[62] randomized 40 patients with acute cholecystitis to undergo either laparoscopic or open cholecystectomy and found significantly greater intraoperative and postoperative histamine levels in patients after the former procedure.

Significantly less activation, preserved serum factors and preserved PMN functions all correlate with the clinical observation of fewer postoperative septic complications following laparoscopic surgery. This suggests that a laparoscopic approach might be beneficial in the surgical management of intra-abdominal sepsis or peritonitis. However, the effect of increased intra-abdominal pressure, and a higher incidence of bacteraemia and systemic inflammatory response, necessitate further investigation of this issue[63].

Delayed-type hypersensitivity and T-cell function

DTH responses reflect alterations in T-lymphocyte populations in patients undergoing surgical procedures. However, DTH is a complex multifactorial phenomenon involving interactions among both lymphocytes and lymphocyte subpopulations which can affect the final response. Although several studies have demonstrated that DTH is better preserved after laparoscopic surgery than after open operation, it is still not clear which component of the whole cascade is responsible for this preservation of cellular immunological response[36].

T cell-related immune function has been examined by assessing DTH response; it is significantly depressed following laparotomy[64]. Gutt *et al.*[65] assessed cell-mediated immune function by measuring the size of skin pustules induced by the intradermal injection of *Staphylococcus aureus* 502A in rats undergoing laparoscopically assisted and open caecal resection. They observed that animals having laparoscopic procedures had both significantly smaller and more rapidly healing pustules than their open surgical counterparts. Similarly, Allendorf *et al.*[18] investigated cell-mediated immune function following laparoscopically assisted and open bowel resections in rats using DTH responses to keyhole limpet haemocyanin and phytohaemagglutinin antigens. The DTH responses to both of these antigens at 24 and 48 h after operation were significantly greater after laparoscopically assisted resection than after open surgery, but these differences were no longer evident on the third postoperative day. Allendorf *et al.*[3] also measured the effect of incision length and exposure method for caecal resection on postoperative immune function as assessed by DTH response. Rats underwent laparotomy (7-cm incision), minilaparotomy (3·5 cm), or laparoscopy (four ports). The responses following laparoscopic surgery were 20 per cent greater than those after open surgery with a long incision, indicating better preservation of systemic cell-mediated immunity. The responses after minilaparotomy were not significantly different to those in either of the other groups.

Gitzelmann *et al.*[19] compared the cell-mediated immune response following carbon dioxide pneumoperitoneum, extraperitoneal incision and laparotomy in an animal model, and demonstrated that cellular immunity as measured by DTH responses and the ability to reject an immunogenic tumour were better preserved after carbon dioxide pneumoperitoneum than after extraperitoneal incision or laparotomy. Significant suppression of *in vivo* cell-mediated immune response was found by Di Vita *et al.*[20] after open cholecystectomy but not after laparoscopic surgery. Other studies have also demonstrated that laparoscopic operation is associated with less impairment of cell-mediated immunity than open surgery[4,21,26].

Decreased T-cell function has been reported by several investigators following surgical stress[66–68]. Surgical stress induces an increase in the peripheral blood lymphocyte subsets that depress cellular immunity, and a decrease in the subsets that promote it. It is also associated with a decreased number of lymphocytes and poorer function[69]. As in the study by Kase *et al.*[70], Ogawa *et al.*[69] also found a decrease in the helper-inducer T, cytotoxic T, NK and IL-2R-positive cell numbers immediately after operation. In contrast, the numbers of suppressor T cells increased after the second postoperative day. Katano *et al.*[71] reported that the decrease in the number of T lymphocytes after operation is due mainly to reduced numbers of $CD3^+$ and $CD4^+$ cells. $CD4^+$ Th cells are important as they play a key role in various immune reactions and can be classified into Th1 and Th2 cells. Th1 cells increase cellular immunity by the production of IL-2, IFN-α and TNF, whereas Th2 cells induce specific antibody production from B cells by producing IL-4, IL-5, IL-6, IL-10 and IL-13[72,73].

Surgical stress also causes a shift in the balance of Th1–Th2 cells towards Th2, suggesting that cell-mediated immunity is downregulated after operation[69]. Downregulation of cell-mediated immunity increases susceptibility to viruses and intracellular bacteria. The increase in Th2 and reduction in Th1 is more pronounced after open than laparoscopic surgery[27,74]. Similar to other reports[69,75–78], Hansbrough *et al.*[79] also reported a relative decrease in the percentage of Th cells and an increased percentage of T suppressor cells following open operation.

Studies reported to date clearly indicate that T-cell function and cell-mediated immunity are better preserved after laparoscopic than after open surgery, although yet again most of the clinical studies have investigated laparoscopic *versus* open cholecystectomy, and caution must be exercised when extrapolating these results to other clinical scenarios.

Monocyte function

The monocyte–macrophages phagocytose infected or altered cells and are the principal source of TNF and IL-1 following T-cell stimulation. They also play an important role in the recognition and processing of foreign antigen, thereby helping to present antigen to leucocytes. The human leucocyte antigen (HLA)-DR (major histocompatibility protein class II) antigen, expressed on the surface of the monocyte–macrophage, is critical in this process[80]. A significant reduction in HLA-DR expression has been reported after open operation, but not after laparoscopic surgery[11,22,23,74]. However, Brune and colleagues[22] found that this decrease in monocyte HLA-DR expression did not alter the antigen-presenting capacity of monocytes in either surgical group. Klava *et al.*[81] assessed the potential role of IFN-γ as a biological prophylactic antiseptic agent (by increasing monocyte HLA-DR expression), by determining the capacity of monocytes to respond following open and laparoscopic surgical procedures of a similar magnitude. They observed that laparoscopic surgery is associated with a similar level of suppression of monocyte HLA-DR expression to that seen after open operation, and this expression is relatively refractory to further stimulation by IFN-γ. This study is consistent with other reports[22] that have demonstrated similar suppression but with earlier return to normal levels following laparoscopic surgery compared with open operation.

Kupffer cells (liver macrophages) are important in the elimination of micro-organisms, antigens and endotoxin arising from the gastrointestinal tract[82]. They have also been shown to modulate the local and systemic immune responses by releasing cytokines[82–84]. Monocyte-mediated cytotoxicity correlates closely with Kupffer cell-mediated cytotoxicity and both of these cells play a key role in limiting tumour growth in the liver[24]. Vittimberga *et al.*[85] observed no difference in cytokine response following laparoscopy and open surgery. However, intracellular Kupffer cell signalling was slightly different between laparoscopy and laparotomy. On the other hand Sietses *et al.*[24] investigated three different laparoscopic procedures and demonstrated that monocyte-mediated cytotoxicity was suppressed following conventional but not laparoscopic surgery.

Several clinical and experimental studies have shown that the mononuclear phagocyte system (MPS) plays an important part in physiological defence against tumour metastases and bacterial infection. Gutt *et al.*[25] investigated the phagocytic activity of the rat MPS by means of an intravascular carbon clearance test during conventional and laparoscopic fundoplication using pneumoperitoneum and gasless laparoscopy. Although the fastest carbon elimination half-life was found in rats undergoing gasless laparoscopy, the carbon clearance half-life after conventional laparoscopy was significantly greater than that associated with open surgery.

Lymphocyte subpopulation studies

Peripheral lymphocytes are the effectors of cellular immunity. When the host is exposed to surgical stress, the number of granulocytes increases, whereas the number of lymphocytes starts decreasing in peripheral blood[69]. Very little is known about changes in NK cells following laparoscopic surgery. However, depressed NK cellular immunity occurs after surgical stress and this may reduce resistance to viable tumour cells. Cristaldi *et al.*[76] found a reduction in NK cell numbers following both open and laparoscopic surgery. However, the reduction was less after the latter on the first postoperative day. In an experimental study, decreased NK cell cytotoxicity was noted following both laparoscopic and open procedures, with no advantage for the laparoscopic approach[86]. Cristaldi *et al.*[76] reported a lower total lymphocyte count after conventional surgery compared with the equivalent laparoscopic approach. They also demonstrated persistent depression of $CD4^+$ cells following conventional surgery, but not after laparoscopic surgery.

Lennard *et al.*[1] classified operations as major or minor according to the severity of the procedure and assessed the effect of open surgery on lymphocyte subpopulations. Based on this classification, open cholecystectomy was categorized as major surgery. Evrard *et al.*[75] applied Lennard's classification and compared changes in lymphocyte subpopulations following laparoscopic and open cholecystectomy, demonstrating that changes after laparoscopic cholecystectomy were equivalent to those seen in Lennard's minor surgery group classification.

In an experimental study, Lee *et al.*[28] compared lymphocyte proliferation rates following laparotomy and carbon dioxide insufflation and found a significantly lower lymphocyte proliferation rate after laparotomy. Interestingly, no difference was found between insufflation and the anaesthesia-only control group at any point in time. Extending their work further, these authors also demonstrated[87] that the lower lymphocyte proliferation rate following open surgery was not dependent on the atmospheric environment, as they found no significant difference between laparotomy performed in room air or in a sealed carbon dioxide chamber. However, in this study the lymphocyte proliferation rate was again significantly greater after laparoscopy.

If all the studies that have investigated systemic immunological function following laparoscopic and open

Table 1 Effect of surgery on components of the systemic immune response

Marker of systemic immune response	Changes following open surgery	Changes following laparoscopy
CRP	↑↑↑	↑
IL-1	↑↑	↑
IL-6	↑↑↑	↑
IL-8	↑↑	↑
IL-10	Data unclear	Data unclear
TNF	Data unclear	Data unclear
Fibrinogen, transferrin	Data unclear	Data unclear
Elastase	↑	↑ (returns to preop. levels early)
Albumin	Data unclear	Data unclear
PMN number	↑↑	↑
PMN function	↓↓	↓
Delayed hypersensitivity	↓↓↓	↓
Th1, Th2	↓↓	↓
CD4^{+}/CD8^{+}	↓↓	↓
Monocyte HLA-DR expression	↓↓↓	↓
Monocyte-mediated cytotoxicity	↓↓	↓
Kupffer cell activity	Data unclear	Data unclear
NK cell number and function	↓	↓

CRP, C-reactive protein; HLA, human leucocyte antigen; IL, interleukin; PMN, polymorphonuclear neutrophil; NK, natural killer; Th, T helper cell; TNF, tumour necrosis factor

surgery in both experimental models and in clinical settings are considered together, their outcomes have consistently demonstrated that surgery is associated with significant depression of overall immune status. Furthermore, the magnitude of this depression appears to be proportional to the length of the wound used to access the peritoneal cavity. Possibly for this reason laparoscopic approaches are associated with less overall disturbance of systemic immune function[5,18,88,89] (*Table 1*).

Intraperitoneal immune function

The benefit of less systemic immune system suppression following laparoscopic surgery[5,18,88,89] may not necessarily be mirrored at the level of the peritoneal membrane. Apart from mechanical factors, the choice of insufflation gas and intraperitoneal pressure are also known to modulate the local immune environment[90,91]. The peritoneal membrane plays a major role in the immunological response to abdominal surgery[92,93]. Badia *et al.*[93] observed sequentially raised cytokine levels in peritoneal fluid following laparotomy and suggested that the systemic postoperative cytokine response may arise from the peritoneal cavity. Similarly, falls in perioperative and postoperative TNF-α levels have also been observed[75].

Peritoneal macrophages play an integral role in the primary inflammatory response to infection and cancer within the abdominal cavity[94]. The scavenging action of these macrophages is mediated in part by the production of inflammatory cytokines, such as TNF-α. Therefore, these cytokines may have a role in host defence[95,96]. The use of carbon dioxide as the insufflating agent has been associated in some experimental studies with impaired production of TNF-α by peritoneal macrophages[94,97,98]. This impaired function may inhibit effective scavenging of viable cells or bacteria liberated during laparoscopic surgery.

Mathew *et al.*[99] found that peritoneal macrophages harvested from rats that had undergone laparoscopy with carbon dioxide 24 h earlier produced significantly less TNF-α *in vivo* than macrophages from rats that had undergone gasless laparoscopy or laparotomy. Furthermore, this response was still present when macrophages were collected 3 days after operation[100]. Similar *in vitro* experiments performed by West *et al.*[101] yielded similar results. Intraperitoneal environmental changes, such as decreased temperature and reduced humidity, may also play a role in the complex intraperitoneal immune cascade. Significant, but temporary, impairment of intraperitoneal macrophage function following laparotomy has also been reported[92]. Hajri *et al.*[102] assessed systemic and peritoneal immune function in rats and found that, with the exception of serum IL-1β, the levels of TNF-α, IL-6 and inducible nitric oxide synthase gene transcription were significantly enhanced in white blood cells and depressed in peritoneal cells. They also noted a strong early impairment of peritoneal macrophage immune activity following carbon dioxide pneumoperitoneum.

The exposure of macrophages to carbon dioxide also causes impaired responsiveness to lipopolysaccharide (endotoxin)[97,98], without affecting cell viability[97]. Such exposure has also been shown significantly to attenuate the cancer cell lysis activity of macrophages[97]. Using a human monocyte line, Jackson and Evans[94] found that exposure to a high concentration of carbon dioxide reduces macrophage cytokine secretion and phagocyte activity, and substantially reduces cytotoxic activity against colonic cancer cells. Exposure of cancer cells to this gas also causes significant acidification of the tumour microenvironment. This might be associated with a higher tumour growth rate compared with that of cells exposed to a helium-rich environment[103]. However, Evrard *et al.*[75] found no change in the lymphocyte viability and no evidence of lymphocyte lysis after using carbon dioxide pneumoperitoneum during laparoscopic procedures. They suggested that this might be because of increased local (peritoneal) bicarbonate production, leading to buffering of the effect produced by carbon dioxide. They also showed that peritoneal lymphocytes were not destroyed by 1 h of pneumoperitoneum during laparoscopic cholecystectomy, whereas circulating lymphocyte subpopulations and cytokine levels were moderately suppressed. More efficient peritoneal bacterial clearance by macrophages after laparoscopic surgery compared with open surgery has also been demonstrated by Collet *et al.*[5]. This study also demonstrated less activation of humoral and peritoneal defences, which the authors believed leads to improved handling of a peritoneal septic challenge[5].

Additional factors might also influence peritoneal immunity, including the temperature of the insufflation gas. Puttick *et al.*[104] compared the immunological and physiological effects of conventional carbon dioxide insufflation at room temperature with carbon dioxide pneumoperitoneum at body temperature. They observed greater levels of cytokines (TNF, IL-1, IL-6) in the peritoneal fluid following pneumoperitoneum at room temperature.

Immune function at the peritoneal level is very complex and, apart from tissue trauma, mechanical effects, intraperitoneal pressure and specific characteristics of the insufflation gas, other factors might also influence this function. Based on a limited number of reported studies it appears that the systemic immunological benefits observed after laparoscopic surgery may not apply at the peritoneal level. However, this area has not been subject to the same depth of investigation as systemic immune function; further studies are needed to clarify the issues raised by recently published experimental work.

Tumour growth, metastasis and immune function

Although it is likely that the aetiology of port site metastases is multifactorial, some experimental studies have suggested that local peritoneal immune depression may play an important role in the development of tumour metastases following laparoscopic surgery[5,91,105,106]. To investigate this further, Neuhaus *et al.*[91] evaluated the effect of immune modulation within an established laparoscopic cancer model, using either systemic cyclosporin (immune suppresser), intraperitoneal endotoxin (immune enhancer) or no agent (control). They demonstrated less tumour growth and fewer port site metastases following the administration of intraperitoneal endotoxin.

Several investigators have demonstrated that the incidence of port site metastases can be reduced in experimental models by the exclusion of carbon dioxide from the laparoscopic environment by using either gasless laparoscopy or insufflation with helium[105,107–109]. This suggests that carbon dioxide, in particular, may exert a metabolic effect on tumour cells that facilitates their implantation and growth. Jacobi *et al.*[110] investigated the impact of different laparoscopic environments on immunological function and tumour growth in a rat model. They found that carbon dioxide significantly promoted tumour growth, and that this increased growth is associated with a significant increase in plasma levels of IL-10 and a decrease in TNF-α concentration in the postoperative period, compared with the situation with helium insufflation. Similar outcomes have been demonstrated by Neuhaus *et al.*[100,111].

Cell-mediated immunity is also believed to influence postoperative tumour growth. Allendorf *et al.*[29] observed significantly less growth of extra-abdominal tumour following laparoscopy compared with open surgery in immunocompetent mice. However, the tumour grew much faster, and the difference between laparoscopy and open surgery was lost, in an athymic mice model. The alterations in ventilatory, cellular, hormonal and immunological parameters[112,113] that occur with pneumoperitoneum may facilitate tumour implantation and growth. Insufflation of carbon dioxide is associated with *in vitro* and *in vivo* growth enhancement[106,109], and may exert an adverse metabolic effect on cells that facilitates tumour implantation and metastasis[105,111].

Conclusion

Despite a few contradictory reports, most clinical and experimental studies support the view that laparoscopic surgery is associated with better preservation of postoperative systemic immune function than conventional surgery. However, the applicability of animal studies to the clinical situation, and the clinical significance of better preserved immunity in terms of postsurgical outcome, require further elucidation. Furthermore, intraperitoneal immunity is complex, and this component of the immune system may behave independently of systemic immune function; the systemic benefits of laparoscopic surgery may not necessarily extend to the peritoneal interface. This might have relevance for laparoscopic techniques in the management of cancer or sepsis. The systemic immunological benefits of laparoscopic surgery will be irrelevant if alterations to the local immune environment are associated with adverse effects that outweigh these benefits. Nevertheless, local peritoneal immunity has been less well studied than its systemic counterpart and further investigation is needed to confirm the results of recently published studies. Ultimately, randomized clinical trials may be needed to determine whether the potential adverse local immunological effects of carbon dioxide insufflation are clinically relevant.

References

1 Lennard TWJ, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM *et al.* The influence of surgical operations on components of the human immune system. *Br J Surg* 1985; **72:** 771–6.

2 Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci* 1990; **79:** 161–5.

3 Allendorf JD, Bessler M, Whelan RL, Trokel M, Laird DA, Terry MB *et al.* Postoperative immune function varies inversely with the degree of surgical trauma in a murine model. *Surg Endosc* 1997; **11:** 427–30.

4 Redmond HP, Watson RW, Houghton T, Condron C, Watson RG, Bouchier-Hayes D. Immune function in patients undergoing open *v* laparoscopic cholecystectomy. *Arch Surg* 1994; **129:** 1240–6.

5 Collet D, Vitale GC, Reynolds M, Klar E, Cheadle WG. Peritoneal host defenses are less impaired by laparoscopy than by open operation. *Surg Endosc* 1995; **9:** 1059–64.

6 Roumen RM, van Meurs PA, Kuypers HH, Kraak WA, Sauerwein RW. Serum interleukin-6 and C reactive protein responses in patients after laparoscopic or conventional cholecystectomy. *Eur J Surg* 1992; **158:** 541–4.

7 Karayiannakis AJ, Makri GG, Mantzioka A, Karousos D, Karatzas G. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg* 1997; **84:** 467–71.

8 Jakeways MS, Mitchell V, Hashim IA, Chadwick SJ, Shenkin A, Green CJ *et al.* Metabolic and inflammatory responses after open or laparoscopic cholecystectomy. *Br J Surg* 1994; **81:** 127–31.

9 Halevy A, Lin G, Gold-Deutsch R, Lavi R, Negri M, Evans S *et al.* Comparison of serum C-reactive protein concentrations for laparoscopic *versus* open cholecystectomy. *Surg Endosc* 1995; **9:** 280–2.

10 Squirrell DM, Majeed AW, Troy G, Peacock JE, Nicholl JP, Johnson AG. A randomized, prospective, blinded comparison of postoperative pain, metabolic response, and perceived health after laparoscopic and small incision cholecystectomy. *Surgery* 1998; **123:** 485–95.

11 Sietses C, Wiezer MJ, Eijsbouts QA, Beelen RH, van Leeuwen PA, von Blomberg BM *et al.* A prospective randomized study of the systemic immune response after laparoscopic and conventional Nissen fundoplication. *Surgery* 1999; **126:** 5–9.

12 Holub Z, Jabor A, Fischlova D, Palasek V, Shomani A. Evaluation of perioperative stress after laparoscopic and abdominal hysterectomy in premalignant and malignant disease of the uterine cervix and corpus. *Clin Exp Obstet Gynecol* 1999; **26:** 12–15.

13 Fornara P, Doehn C, Seyfarth M, Jocham D. Why is urological laparoscopy minimally invasive? *Eur Urol* 2000; **37:** 241–50.

14 Leung KL, Lai PB, Ho RL, Meng WC, Yiu RY, Lee JF *et al.* Systemic cytokine response after laparoscopic-assisted resection of rectosigmoid carcinoma. A prospective randomized trial. *Ann Surg* 2000; **231:** 506–11.

15 Kuntz C, Wunsch A, Bay F, Windeler J, Glaser F, Herfarth C. Prospective randomized study of stress and immune response after laparoscopic *vs* conventional colonic resection. *Surg Endosc* 1998; **12:** 963–7.

16 Kishi D, Nezu R, Ito T, Taniguchi E, Momiyama T, Obunai S *et al.* Laparoscopic-assisted surgery for Crohn's disease: reduced surgical stress following ileocolectomy. *Surg Today* 2000; **30:** 219–22.

17 Sietses C, Wiezer MJ, Eijsbouts QA, van Leeuwen PA, Beelen RH, Meijer S *et al.* The influence of laparoscopic surgery on postoperative polymorphonuclear leukocyte function. *Surg Endosc* 2000; **14:** 812–16.

18 Allendorf JD, Bessler M, Whelan RL, Trokel M, Laird DA, Terry MB *et al.* Better preservation of immune function after laparoscopic-assisted *vs* open bowel resection in a murine model *Dis Colon Rectum* 1996; 39(Suppl): S67–72.

19 Gitzelmann CA, Mendoza-Sagaon M, Talamini MA, Ahmad SA, Pegoli W Jr, Paidas CN. Cell-mediated immune response is better preserved by laparoscopy than laparotomy. *Surgery* 2000; **127:** 65–71.

20 Di Vita G, Sciume C, Lauria G, Stella C, Di Bella G. Cell-mediated immunity after laparoscopic cholecystectomy. *Surg Endosc* 2000; **14:** S17 (Abstract).

21 Griffith JP, Everitt NJ, Lancaster F, Boylston A, Richards SJ, Scott CS *et al.* Influence of laparoscopic and conventional cholecystectomy upon cell mediated immunity. *Br J Surg* 1995; **82:** 677–80.

22 Brune IB, Wilke W, Hensler T, Feussner H, Holzmann B, Siewert JR. Normal T lymphocyte and monocyte function after minimally invasive surgery. *Surg Endosc* 1998; **12:** 1020–4.

23 Kloosterman T, von Blomberg BM, Borgstein P, Cuesta MA, Scheper RJ, Meijer S. Unimpaired immune functions after laparoscopic cholecystectomy. *Surgery* 1994; **115:** 424–8.

24 Sietses C, Havenith CE, Eijsbouts QA, van Leeuwen PA, Meijer S, Beelen RH *et al.* Laparoscopic surgery preserves

monocyte-mediated tumor cell killing in contrast to the conventional approach. *Surg Endosc* 2000; **14:** 456–60.

25 Gutt CN, Heinz P, Kaps W, Paolucci V. The phagocytosis activity during conventional and laparoscopic operations in the rat. A preliminary study. *Surg Endosc* 1997; **11:** 899–901.

26 Gleason NR, Blanco I, Allendorf JD, Lee SW, Zhai C, Bessler M *et al.* Delayed type hypersensitivity response is better preserved in mice following insufflation than after laparotomy. *Surg Endosc* 1999; **13:** 1032–4.

27 Decker D, Lindemann C, Springer W, Low A, Hirner A, von Ruecker A. Endoscopic *vs* conventional hernia repair from an immunologic point of view. *Surg Endosc* 1999; **13:** 335–9.

28 Lee SW, Southall JC, Gleason NR, Huang EH, Bessler M, Whelan RL. Time course of differences in lymphocyte proliferation rates after laparotomy *versus* CO_2 insufflation. *Surg Endosc* 2000; **14:** 145–8.

29 Allendorf JD, Bessler M, Horvath KD, Marvin MR, Laird DA, Whelan RL. Increased tumor establishment and growth after open *vs* laparoscopic surgery in mice may be related to differences in postoperative T-cell function. *Surg Endosc* 1999; **13:** 233–5.

30 Grace PA, Quereshi A, Coleman J, Keane R, McEntee G, Broe P *et al.* Reduced postoperative hospitalization after laparoscopic cholecystectomy. *Br J Surg* 1991; **78:** 160–2.

31 Faist E, Kupper TS, Baker CC, Chaudry IH, Dwyer J, Baue AE. Depression of cellular immunity after major injury. Its association with posttraumatic complications and its reversal with immunomodulation. *Arch Surg* 1986; **121:** 1000–5.

32 Slade MS, Simmons RL, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. *Surgery* 1975; **78:** 363–72.

33 Ohzato H, Yoshizaki K, Nishimoto N, Ogata A, Tagoh H, Monden M *et al.* Interleukin-6 as a new indicator of inflammatory status: detection of serum levels of interleukin-6 and C-reactive protein after surgery. *Surgery* 1992; **111:** 201–9.

34 Decker D, Lindemann C, Low A, Bidlingmaier F, Hirner A, von Ruecker A. Changes in the cytokine concentration (IL-6, IL-8, IL-1ra) and their cellular expression of membrane molecules (CD25, CD30, HLA-DR) after surgical trauma. *Zentralbl Chir* 1997; **122:** 157–64.

35 van Dijk WC, Verbrugh HA, van Rijswijk RE, Vos A, Verhoef J. Neutrophil function, serum opsonic activity, and delayed hypersensitivity in surgical patients. *Surgery* 1982; **92:** 21–9.

36 Vittimberga FJ Jr, Foley DP, Meyers WC, Callery MP. Laparoscopic surgery and the systemic immune response. *Ann Surg* 1998; **227:** 326–34.

37 Mayers I, Johnson D. The nonspecific inflammatory response to injury. *Can J Anaesth* 1998; **45:** 871–9.

38 Pike GK, Bessell JR, Mathew G, Watson DI, Mitchell PC, Jamieson GG. Changes in fibrinogen levels in patients undergoing open and laparoscopic Nissen fundoplication. *Aust N Z J Surg* 1996; **66:** 94–6.

39 Vander Velpen G, Penninckx F, Kerremans R, Van Damme J, Arnout J. Interleukin-6 and coagulation fibrinolysis fluctuations after laparoscopic and conventional cholecystectomy. *Surg Endosc* 1994; **8:** 1216–20.

40 McMahon AJ, O'Dwyer PJ, Cruikshank AM, McMillan DC, O'Reilly DS, Lowe GD *et al.* Comparison of metabolic responses to laparoscopic and minilaparotomy cholecystectomy. *Br J Surg* 1993; **80:** 1255–8.

41 Glaser F, Sannwald GA, Buhr HJ, Kuntz C, Mayer H, Klee F *et al.* General stress response to conventional and laparoscopic cholecystectomy. *Ann Surg* 1995; **221:** 372–80.

42 Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P *et al.* Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *Br J Anaesth* 1992; **69:** 341–5.

43 Mealy K, Gallagher H, Barry M, Lennon F, Traynor O, Hyland J. Physiological and metabolic response to open and laparoscopic cholecystectomy. *Br J Surg* 1992; **79:** 1061–4.

44 Perlmutter DH, Dinarello CA, Punsal PI, Colten HR. Cachectin/tumor necrosis factor regulates hepatic acute-phase gene expression. *J Clin Invest* 1986; **78:** 1349–54.

45 van Zee KJ, Kohno T, Fischer E, Rock CS, Moldawer LL, Lowry SF. Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor-α *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 1992; **89:** 4845–9.

46 Sakamoto K, Arakawa H, Mita S, Ishiko T, Ikei S, Egami H *et al.* Elevation of circulating interleukin 6 after surgery: factors influencing the serum level. *Cytokine* 1994; **6:** 181–6.

47 Cosgrove JM, Cai S, Korman J, Rao S. Serum cytokine (IL-6) response in open and laparoscopic cholecystectomy. *Surg Endosc* 1996; **10:** 228 (Abstract).

48 Schwenk W, Jacobi C, Mansmann U, Bohm B, Muller JM. Inflammatory response after laparoscopic and conventional colorectal resections – results of a prospective randomized trial. *Langenbecks Arch Surg* 2000; **385:** 2–9.

49 Johnson DRE, Spencer MP, Cerra FB, Konstantidides F, Rothenberger DA, Madoff RD. Laparoscopic *versus* open colectomy: a comparative study of systemic stress response. *Surg Endosc* 1994; **8:** 447 (Abstract).

50 Stage JG, Schulze S, Moller P, Overgaard H, Anderson M, Rebsdorf-Pedersen VB *et al.* Prospective randomized study of laparoscopic *versus* open colonic resection for adenocarcinoma. *Br J Surg* 1997; **84:** 391–6.

51 Hill AD, Banwell PE, Darzi A, Menzies-Gow N, Monson JRT, Guillou PJ. Inflammatory markers following laparoscopic and open hernia repair. *Surg Endosc* 1995; **9:** 695–8.

52 Akhtar K, Kamalky-asl ID, Lamb WR, Laing I, Walton L, Pearson RC *et al.* Metabolic and inflammatory responses after laparoscopic and open inguinal hernia repair. *Ann R Coll Surg Engl* 1998; **80:** 125–30.

53 Hildebrandt U, Kessler K, Pistorius G, Lindemann W, Ecker KW, Feifel G *et al.* Granulocyte elastase and systemic cytokine response after laparoscopic-assisted and open resections in Crohn's disease. *Dis Colon Rectum* 1999; **42:** 1480–6.

54 Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998; **115:** 182–205.

55 Stallmach A, Strober W, MacDonald TT, Lochs H, Zeitz M. Induction and modulation of gastrointestinal inflammation. *Immunol Today* 1998; **19:** 438–41.

56 Polk HC Jr, George CD, Hershman MJ, Wellhausen SR, Cheadle WG. The capacity of serum to support neutrophil phagocytosis is a vital host defense mechanism in severely injured patients. *Ann Surg* 1988; **207:** 686–92.

57 Cohen IR, Sciutto MS, Brown GL, Polk HC Jr. Failure of opsonization as a sign of lethal sepsis. *J Infect Dis* 1984; **149:** 651.

58 Maruszynski M, Pojda Z. Interleukin-6 (IL-6) levels in the monitoring of surgical trauma. A comparison of serum IL-6 concentrations in patients treated by cholecystectomy via laparotomy or laparoscopy. *Surg Endosc* 1995; **9:** 882–5.

59 Gal I, Lantos L, Roth E. Changes of PMN elastase and C-reactive protein following traditional and laparoscopic cholecystectomy. *Surg Endosc* 1996; **10:** 552 (Abstract).

60 Freyer DR, Morganroth ML, Rogers CE, Arnaout MA, Todd RF III. Modulation of surface CD11/CD18 glycoproteins (MO1, LFA-1, P150, 95) by human mononuclear phagocytes. *Clin Immunol Immunopathol* 1988; **46:** 272–83.

61 Carey PD, Wakefield CH, Thayeb A, Monson JR, Darzi A, Guillou PJ. Effects of minimally invasive surgery on hypochlorous acid production by neutrophils. *Br J Surg* 1994; **81:** 557–60.

62 Nies C, Krack W, Lorenz W, Kaufmann T, Sitter H, Celik I *et al.* Histamine release in conventional *versus* minimally invasive surgery: results of a randomised trial in acute cholecystitis. *Inflamm Res* 1997; **46**(Suppl 1): S83–4.

63 Tsilibary EC, Wissig SL. Lymphatic absorption from peritoneal cavity: regulation of patency of mesothelial stomata. *Microvasc Res* 1983; **25:** 22–39.

64 Little D, Regan M, Keane RM, Bouchier-Hayes D. Perioperative immune modulation. *Surgery* 1993; **114:** 87–91.

65 Gutt CN, Kuntz C, Schmandra T, Wunsch A, Heinz P, Bouvy N *et al.* Metabolism and immunology in laparoscopy. First workshop on experimental laparoscopic surgery, Frankfurt, 1997. *Surg Endosc* 1998; **12:** 1096–8.

66 Shafir M, Bekesi JG, Papatestas A, Slater G, Aufses AH Jr. Preoperative and postoperative immunological evaluation of patients with colorectal cancer. *Cancer* 1980; **46:** 700–5.

67 Nakata Y, Nabeya K, Hanaoka T, Kaku C, Kimura O, Kobayashi H. Influence of surgical stress of esophageal cancer on cell mediated immunity: comparison with surgical stress of gastric cancer. *Jpn J Gastroenterol Surg* 1993, **26:** 1204–10.

68 Brune IB, Wilke W, Hensler T, Holzmann B, Siewert JR. Downregulation of T helper type 1 immune response and altered pro-inflammatory and anti-inflammatory T cell cytokine balance following conventional but not laparoscopic surgery. *Am J Surg* 1999; **177:** 55–60.

69 Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T *et al.* Suppression of cellular immunity by surgical stress. *Surgery* 2000; **127:** 329–36.

70 Kase H, Kobayashi K, Honda R, Washizawa N, Satoh Y, Nagasawa S *et al.* Influence of surgical stress on immunological activity in patients with gastric cancer and an attempt on the effect of early recovery by pre-operative immunotherapy. *Jpn J Gastroenterol Surg* 1991; **24:** 1938–46.

71 Katano M, Nagumo F, Yamamoto H, Hisatsugu T, Tadano L. Effect of operation on host cellular immunity. *Biotherapy* 1993; **7:** 711–13.

72 Romagnani S. Induction of T(H)1 and T(H)2 responses: a key role for 'natural' immune response? *Immunol Today* 1992; **13:** 379–81.

73 Banchereau J, Blanchard D, Briere F, Liu YJ. Molecular control of B-cell immunopoiesis. *Ann N Y Acad Sci* 1994; **725:** 22–33.

74 Decker D, Schondorf M, Bidlingmaier F, Hirner A, von Ruecker AA. Surgical stress induces a shift in the type 1/type 2 T-helper cell balance, suggesting down-regulation of cell mediated and up-regulation of antibody-mediated immunity commensurate to the trauma. *Surgery* 1996; **119:** 316–25.

75 Evrard S, Falkenrodt A, Park A, Tassetti V, Mutter D, Marescaux J. Influence of CO_2 pneumoperitoneum on systemic and peritoneal cell-mediated immunity. *World J Surg* 1997; **21:** 353–7.

76 Cristaldi M, Rovati M, Elli M, Gerlinzani S, Lesma L, Balzarotti L *et al.* Lymphocytic subpopulation changes after open and laparoscopic cholecystectomy: a prospective and comparative study on 38 patients. *Surg Laparosc Endosc* 1997; **7:** 255–61.

77 Vallina VL, Velasco JM. The influence of laparoscopy on lymphocyte subpopulations in the surgical patient. *Surg Endosc* 1996; **10:** 481–4.

78 Dionigi R, Dominioni L, Benevento A, Giudice G, Cuffari S, Bordone N *et al.* Effect of surgical trauma of laparoscopic *vs* open cholecystectomy. *Hepatogastroenterology* 1994; **41:** 471–6.

79 Hansbrough JF, Bender EM, Zapata-Sirvent R, Anderson J. Altered helper and suppressor lymphocyte populations in surgical patients. A measure of postoperative immunosuppression. *Am J Surg* 1984; **148:** 303–7.

80 Johnston RB Jr. Current concepts: immunology. Monocytes and macrophages. *N Engl J Med* 1988; **318:** 747–52.

81 Klava A, Windsor A, Boylston AW, Reynolds JV, Ramsden CW, Guillou PJ. Monocyte activation after open and laparoscopic surgery. *Br J Surg* 1997; **84:** 1152–6.

82 Rogoff TM, Lipsky PE. Role of the Kupffer cells in local and systemic immune responses. *Gastroenterology* 1981; **80:** 854–60.

83 Callery MP, Kamei T, Flye MW. Endotoxin stimulates interleukin-6 production by human Kupffer cells. *Circ Shock* 1992; **37:** 185–8.

84 Decker T, Lohmann-Matthes ML, Krack U, Peters T, Decker K. Comparative study of cytotoxicity, tumor necrosis factor, and prostaglandin release after stimulation of rat

Kupffer cells, murine Kupffer cells, and murine inflammatory liver macrophages. *J Leukoc Biol* 1989; **45:** 139–46.

85 Vittimberga FJ, Nolan B, Perugini RA, Spector L, Callery MP. Laparoscopic surgery and Kupffer cell activation. *Surg Endosc* 2000; **14:** 1171–6.

86 Sandoval BA, Robinson AV, Sulaiman TT, Shenk RR, Stellato TA. Open *versus* laparoscopic surgery: a comparison of natural antitumoral immunity in a small animal model. *Am Surg* 1996; **62:** 625–31.

87 Lee SW, Southall JC, Gleason NR, Huang EH, Bessler M, Whelan RL. Lymphocyte proliferation in mice after a full laparotomy is same whether performed in a sealed carbon dioxide chamber or in room air. *Surg Endosc* 2000; **14:** 235–8.

88 Allendorf JD, Bessler M, Kayton ML, Oesterling SD, Treat MR, Nowygrod R *et al.* Increased tumor establishment and growth after laparotomy *vs* laparoscopy in a murine model. *Arch Surg* 1995; **130:** 649–53.

89 Bouvy ND, Marquet RL, Hamming JF, Jeekel J, Bonjer HJ. Laparoscopic surgery in the rat. Beneficial effect on body weight and tumor take. *Surg Endosc* 1996; **10:** 490–4.

90 Watson RW, Redmond HP, McCarthy J, Burke PE, Bouchier-Hayes D. Exposure of the peritoneal cavity to air regulates early inflammatory responses to surgery in a murine model. *Br J Surg* 1995; **82:** 1060–5.

91 Neuhaus SJ, Watson DI, Ellis T, Rofe AM, Jamieson GG. The effect of immune enhancement and suppression on the development of laparoscopic port site metastases. *Surg Endosc* 2000; **14:** 439–43.

92 Redmond HP, Hofmann K, Shou J, Leon P, Kelly CJ, Daly JM. Effects of laparotomy on systemic macrophage function. *Surgery* 1992; **111:** 647–55.

93 Badia JM, Whawell SA, Scott-Coombes DM, Abel PD, Williamson RC, Thompson JN. Peritoneal and systemic cytokine response to laparotomy. *Br J Surg* 1996; **83:** 347–8.

94 Jackson PG, Evans SRT. Intraperitoneal macrophages and tumor immunity: a review. *J Surg Oncol* 2000; **75:** 146–54.

95 Rofe AM, Bourgeois CS, Coyle P. Beneficial effects of endotoxin treatment on metabolism in tumour-bearing rats. *Immunol Cell Biol* 1992; **70:** 1–7.

96 Jones AL, Selby P. Clinical applications of tumour necrosis factor. *Prog Growth Factor Res* 1989; **1:** 107–22.

97 Puttick MI, Nduka C, Yong L, Darzi A. Macrophage activation and anti-tumour cytotoxicity is impaired following exposure to a carbon dioxide pneumoperitoneum. *Surg Endosc* 1998; **12**(Suppl): S40 (Abstract).

98 West MA, Baker J, Bellingham J. Kinetics of decreased LPS-stimulated cytokine release by macrophages exposed to CO_2. *J Surg Res* 1996; **62:** 269–74.

99 Mathew G, Watson DI, Ellis TS, Jamieson GG, Rofe AM. The role of peritoneal immunity and the tumour-bearing state on the development of wound and peritoneal metastases after laparoscopy. *Aust N Z J Surg* 1999; **69:** 14–18.

100 Neuhaus SJ, Watson DI, Ellis T, Rofe AM, Mathew G, Jamieson GG. Influence of gases on intra-peritoneal immunity during laparoscopy in tumor-bearing rats. *World J Surg* 2000; **24:** 1227–31.

101 West MA, Hackam DJ, Baker J, Rodriguez JL, Bellingham J, Rotstein OD. Mechanism of decreased *in vitro* murine macrophage cytokine release after exposure to carbon dioxide: relevance to laparoscopic surgery. *Ann Surg* 1997; **226:** 179–90.

102 Hajri A, Mutter D, Wacks S, Bastien C, Gury JF, Marescaux J *et al.* Dual effect of laparoscopy on cell-mediated immunity. *Eur Surg Res* 2000; **32:** 261–6.

103 Nduka C, Coates P, Capel M, Mansfield A, Darzi A. Carbon dioxide pneumoperitoneum enhances postoperative tumour growth. *Br J Surg* 1997; **84**(Suppl 1)**:** 25 (Abstract).

104 Puttick MI, Scott-Coombes DM, Dye J, Nduka CC, Menzies-Gow NM, Mansfield AO *et al.* Comparison of immunologic and physiologic effects of CO_2 pneumoperitoneum at room and body temperatures. *Surg Endosc* 1999; **13:** 572–5.

105 Watson DI, Mathew G, Ellis T, Baigrie CF, Rofe AM, Jamieson GG. Gasless laparoscopy may reduce the risk of port-site metastases following laparoscopic tumor surgery. *Arch Surg* 1997; **132:** 166–8.

106 Jacobi CA, Sabat R, Bohm B, Zieren HU, Volk HD, Muller JM. Pneumoperitoneum with carbon dioxide stimulates growth of malignant colonic cells. *Surgery* 1997; **121:** 72–8.

107 Mathew G, Watson DI, Rofe AM, Baigrie CF, Ellis T, Jamieson GG. Wound metastases following laparoscopic and open surgery for abdominal cancer in a rat model. *Br J Surg* 1996; **83:** 1087–90.

108 Mathew G, Watson DI, Rofe AM, Ellis T, Jamieson GG. Adverse impact of pneumoperitoneum on intraperitoneal implantation and growth of tumour cell suspension in an experimental model. *Aust N Z J Surg* 1997; **67:** 289–92.

109 Bouvy ND, Marquet RL, Jeekel H, Bonjer HJ. Impact of gas(less) laparoscopy and laparotomy on peritoneal tumor growth and abdominal wall metastases. *Ann Surg* 1996; **224:** 694–701.

110 Jacobi CA, Wenger F, Sabat R, Volk T, Ordemann J, Muller JM. The impact of laparoscopy with carbon dioxide *versus* helium on immunologic function and tumor growth in a rat model. *Dig Surg* 1998; **15:** 110–16.

111 Neuhaus SJ, Watson DI, Ellis T, Rowland R, Rofe AM, Pike GK *et al.* Wound metastasis after laparoscopy with different insufflation gases. *Surgery* 1998; **123:** 579–83.

112 Volz J, Koster S, Weiss M, Schmidt R, Urbaschek R, Melchert F *et al.* Pathophysiologic features of a pneumoperitoneum at laparoscopy: a swine model. *Am J Obstet Gynecol* 1996; **174:** 132–40.

113 Volz J, Koster S, Melchert F. The effects of pneumoperitoneum on intraperitoneal tumour implantation in nude mice. *Gynaecol Endosc* 1996; **5:** 193–6.

Review

Detection and clinical significance of occult tumour cells in colorectal cancer

G. Tsavellas, H. Patel and T. G. Allen-Mersh

Department of Surgery, Imperial College School of Medicine, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK
Correspondence to: Professor T. G. Allen-Mersh (e-mail: t.allenmersh@ic.ac.uk)

Background: A variety of techniques have been employed for the detection of occult tumour cells in the blood, bone marrow and lymph nodes of patients with colorectal cancer. This review examines the methods used, results obtained and the clinical significance of studies in this field.
Methods: A Medline literature search was performed using the terms colorectal cancer, minimal residual disease, micrometastasis, polymerase chain reaction, reverse transcriptase polymerase chain reaction and immunocytochemistry; further references were obtained from key articles.
Results: Immunocytochemical examination of bone marrow is the benchmark for detecting clinically significant occult disease. Larger standardized studies are required to confirm the prognostic significance of molecular assays for the detection of tumour cells in blood and bone marrow. The prognostic significance of lymph node tumour cells detected by either immunohistochemical or molecular methods awaits further affirmation.
Conclusion: Standardization of terminology and techniques used, combined with large prospective clinical studies, is required if detection of occult residual disease is to become a prognostic marker for recurrence in colorectal cancer.

Paper accepted 16 May 2001

British Journal of Surgery 2001, 88, 1307–1320

Introduction

Approximately 50 per cent of patients who undergo a supposedly curative resection of colorectal cancer die from metastatic disease within 5 years. Adjuvant chemotherapy reduces the mortality rate by up to 22 per cent in poor-risk patients[1], making accurate staging essential. However, staging accuracy has remained largely unchanged since Dukes' original classification of rectal cancer[2,3], with spread to locoregional lymph nodes remaining the most important prognostic indicator available. Thirty per cent of patients with histologically node-negative colorectal cancer eventually relapse and die from disseminated disease that is not detected at the time of primary surgery, showing current staging to be imprecise. Current evidence does not support the use of adjuvant chemotherapy in patients with node-negative tumours[4], but chemotherapy might improve survival in the 30 per cent of these patients who are destined to relapse. The development and validation of methods for the detection of residual occult malignant disease would allow movement away from the concept of adjuvant treatment in patients in whom there may be a high chance of residual disease, towards the treatment of actual residual disease at a time when overall tumour burden is low. Detection of occult disease may help to predict prognosis, assess response to systemic therapy, provide early warning of recurrence and, through timely therapeutic intervention, improve survival.

While there has been a rapid growth of interest in the detection of low-level disseminated malignant disease, this has not been accompanied by the use of standardized terminology. This is exemplified by the common use of the term 'micrometastasis'. A micrometastasis is an independent collection of tumour cells, without a specific blood supply, measuring less than 2 mm in diameter[5]. The term retains a morphological connotation as prerequisites for metastasis are tumour cell arrest, implantation and proliferation with a surrounding stromal reaction, so a micrometastasis can be diagnosed only by histological examination. However, the development of non-morphological tumour cell detection methods has been accompanied by common usage of the term. Furthermore, in the case of morphological methods, distinction between micrometastases and isolated tumour cells could be important as each may have different prognostic implications. The Union Internacional Contra la Cancrum

(UICC) has recently recommended that micrometastases and isolated tumour cells should be classified according to uniform criteria, including a record of the method used in their detection[6]. In this way their prognostic significance can be evaluated before their incorporation into staging classifications, thereby avoiding stage migration[7].

Since metastasis in colorectal cancer occurs mainly via the circulation or lymphatic system, the detection of occult tumour cells has focused on examination of the blood, bone marrow and lymph nodes.

Circulating tumour cells

The question of whether circulating tumour cells represent metastatic dissemination, or are merely cancer cells without metastatic potential that have detached from the primary tumour, has been debated for over half a century. In a 20-year literature review in 1975, Salsbury[8] concluded that 'it would be doubtful that the detection of circulating tumour cells would carry any prognostic value'. However, the emergence of highly sensitive detection methods has rekindled interest in the significance of circulating tumour cells over the past decade.

Immunocytochemical detection of circulating tumour cells

Circulating tumour cells may be detected by immunocytochemical staining with monoclonal antibodies, although only one study dealing with colorectal cancer was identified[9]. Tumour cells were detected in the blood of only three of 42 patients before operation, suggesting that without prior tumour cell enrichment (using epithelium-specific magnetic beads)[10] immunocytochemistry is unlikely to be sufficiently sensitive to detect these circulating cells.

Molecular detection of circulating tumour cells

The polymerase chain reaction (PCR) was reported in 1986[11,12] and by 1991[13] it had been developed for use in tumour cell detection. PCR involves the amplification and detection of tumour-specific DNA mutations in malignant cells. This approach is therefore restricted to tumours harbouring specific mutations. A more common method uses the reverse transcriptase polymerase chain reaction (RT PCR), which involves amplification of tissue-specific messenger RNA (mRNA) present in malignant cells and allows the detection of a single tumour cell present among 10^7 normal cells[14,15]; this represents a level of sensitivity three orders of magnitude greater than immunocytochemistry.

Polymerase chain reaction studies

Using PCR identification of K-*ras* mutations and immunomagnetic enrichment to increase sensitivity, Hardingham *et al.*[16] were able to identify mutations in codon 12 of the K-*ras* gene in the blood of nine of 27 patients with colorectal cancer whose primary tumour carried the same mutation. Thirteen control subjects had negative findings and PCR positivity was associated with significantly reduced disease-free survival on univariate Kaplan–Meier analysis ($P = 0{\cdot}0001$). However, DNA molecules are relatively stable and the detection of tumour-specific mutations in peripheral blood may not necessarily indicate the presence of circulating tumour cells, but rather extracellular fragments of primary or metastatic tumour DNA arising from cell necrosis or apoptosis[17]. Using a PCR assay, Kopreski *et al.*[18] were able to demonstrate the presence of mutant K-*ras* DNA in the serum fraction of blood in 12 of 39 patients with colorectal cancer. Furthermore, although PCR for K-*ras* DNA provides direct evidence of the presence of a malignancy, it cannot be applied routinely because a primary tumour may not contain the K-*ras* codon 12 mutation.

Reverse transcriptase polymerase chain reaction studies

Over 25 RT PCR studies for the detection of circulating colorectal cancer cells were identified (*Table 1*), with cytokeratin markers being the most widely used[19,21,23,24,26–28,30–32,36–40,45]. Cytokeratin (CK) 8, CK18 and (probably) CK19 are expressed in normal blood, which limits their use as markers of circulating tumour cells (*Table 2*); some studies suggest that CK19 mRNA is absent from normal blood[23,46]. Most reports describe an absence of CK20 expression in normal blood[19,23,24,27,28,33,39,40,51,52], but a minority of investigators have raised doubts about CK20 specificity in blood[26,30,33,36]. Although clinical studies targeting circulating CK20 mRNA in colorectal cancer have been low powered because of small sample sizes (*Table 1*), most have suggested an association between preoperative CK20 mRNA positivity and advancing tumour stage[21,27,28,38]. Funaki *et al.*[28] found that 12 patients with recurrent or disseminated colorectal cancer were all positive for CK20 mRNA on peripheral blood analysis, in contrast to only one of seven patients with Dukes' stage A or B disease. Furthermore, none of the latter group developed recurrence during the limited follow-up time of 16 months. Soeth *et al.*[21] also reported that preoperative circulating CK20 mRNA positivity was stage dependent, with significantly shorter survival in CK20 mRNA-positive patients. Using a panel of markers (CK19, CK20, mucins 1 and 2), Hardingham *et al.*[38] detected circulating epithelial cells before operation in 19 (20 per cent) of 94 patients with colorectal cancer; marker mRNA positivity was associated

Table 1 Reverse transcriptase polymerase chain reaction studies on circulating colorectal cancer cells

Reference	Year	Marker	PCR cycles	No. of patients	Positive for CTCs (%)	Median follow-up (months)	Effect of CTC positivity on prognosis	No. of healthy controls	False positives (%)	Volume of blood sampled (ml)	Multiple sampling
Burchill *et al.*[19]*	1995	CK8,	40	0	NA	NA	NA	9	89	NA	No
		CK19,						15	40		
		CK20						15	0		
Mori *et al.*[15]	1996	CEA	50	20	35	NA	NA	22	0	2	No
Jonas *et al.*[20]	1996	CEA	29	31	84	NA	NA	22	23	14	No
Soeth *et al.*[21]	1997	CK20	60	NS†	17	28	'Adverse'	58	3	20	No
Wong *et al.*[22]	1997	CD44	30	24	17	NA	NA	8	0	15	No
Denis *et al.*[23]	1997	CK8, CK19, CK20	60	23	52	NA	NA	26	0	5	No
Funaki *et al.*[24]	1997	CK20	105	8	75	16	NA	3	0	5	No
Mori *et al.*[25]	1998	CEA	50	27	38	24	'Adverse'	22	0	2	No
Wyld *et al.*[26]	1998	CK20	40	25	48	14	NA	12	8	8	No
Weitz *et al.*[27]	1998	CK20	70	65	46	NA	NA	12	0	10	No
Funaki *et al.*[28]	1998	CK20	105	28	64	18	'Adverse'	6	0	5	No
Castells *et al.*[29]	1998	CEA	35	95	41	NA	NA	11	0	20	No
Champelovier *et al.*[30]	1999	CK20	60	5	60	NA	NA	29	72	3–5	No
Weitz *et al.*[31]	1999	CK20	70	16	13	NA	NA	0	0	10	No
Wharton *et al.*[32]	1999	CEA and CK20	29–35	100	74	NA	NA	70	4	14	Yes
Jung *et al.*[33]	1999	CK20	60	NA	NA	NA	NA	33	0	5	No
Noh *et al.*[34]	1999	CEA	NS	24	38	NA	NA	9	0	10–14	No
Patel *et al.*[35]	1999	CK20	29	55	60	12	NA	85	2	14	Yes
Bustin *et al.*[36]	1999	CK19	40	27	26	NA	NA	21	30	3	No
		CK20		27	100			21	100		
		GCC		27	74			21	5		
Funaki *et al.*[37]	2000	CK20	70	8	75	NA	NA	3	0	5	No
Hardingham *et al.*[38]	2000	CK19, CK20, mucin 1 and 2	45	94	20	37	'Adverse'	20	0	20	No
Yamaguchi *et al.*[39]	2000	CEA and CK20	45 60	52	38 (CEA)‡ 36 (CK20)‡	16	'Adverse'	10	0	10	No
Weitz *et al.*[40]	2000	CK20	70	41	63	NA	NA	31	0	10	No
Patel *et al.*[41]	2000	CEA and CK20	29	55	78	12	NA	85	5	14	Yes
Masson *et al.*[42]	2000	CD44v6	70	10	31	NA	NA	6	100	5	Yes
		CK19	40	10	19			NA	NA		
Khan *et al.*[43]	2000	p53	48	41	42	NA	NA	10	0	7	Yes
Taniguchi *et al.*[44]	2000	CEA	50	53	34 68‡	NS	'Adverse'	32	0	10	No

*Cell line 'spiking' study; †total of 52 patients with gastrointestinal malignancy; ‡tumour drainage blood. PCR, polymerase chain reaction; CTC, circulating tumour cell; CK, cytokeratin; CEA, carcinoembryonic antigen; GCC, guanylyl cyclase C; NS, not stated; NA, not assessed

Table 2 Limitations of cytokeratin markers

CK8	Illegitimate transcription in normal bone marrow[46,47]
	Expressed in normal lymph node tissue[46]
	Expressed by polymorphonuclear blood cells[23,46]
CK18	Pseudogene[48]
	Illegitimate transcription in normal bone marrow[46,47]
	Expressed in normal lymph node tissue[46]
	Expressed by polymorphonuclear blood cells[46]
CK19	Pseudogene[49]
	Illegitimate transcription in normal bone marrow[50]
	Expressed in normal lymph node tissue[50]
	Expressed by fibroblasts and endothelial cells (present in bone marrow and lymph nodes)[46]
	Expressed in normal blood[19,36,50]
CK20	Expressed in normal blood[26,30,36]
	Expressed by granulocytes[33]

with reduced disease-free and overall survival ($P = 0{\cdot}0001$, log rank test).

Carcinoembryonic antigen (CEA) mRNA is not thought to be produced by peripheral blood haemopoietic cells[15,20], although ectopic CEA mRNA expression has been reported in bone marrow[47]. Several studies have used CEA mRNA as a target marker to detect circulating tumour cells[15,20,25,29,32,34,39,44]. Preoperative circulating CEA mRNA positivity was associated with advancing Dukes' stage in several studies[15,20,25,29,34,44], but not in others[32,35,41]. Mori *et al.*[25] found a significant increase in subsequent metastasis rates in CEA mRNA-positive patients who had undergone curative surgery for breast, colorectal and a variety of other gastrointestinal cancers ($P < 0{\cdot}01$). More recently, in a study of 53 patients with colorectal cancer, Taniguchi *et al.*[44] found that the 2-year disease-free survival rate of patients positive for CEA mRNA in either venous blood draining from the tumour ($P < 0{\cdot}05$) or peripheral blood ($P < 0{\cdot}01$) was significantly worse than that of those who were negative. Using a combined CEA and CK20 RT PCR assay, Yamaguchi *et al.*[39] found a significant association between a positive result and UICC stage ($P = 0{\cdot}006$) in 52 patients with colorectal cancer. Multivariate analysis indicated that the combined detection of CEA and CK20 mRNA in mesenteric blood draining the tumour before tumour manipulation was an independent prognostic variable.

Although splice variants of the CD44 gene have been targeted in blood[22], the presence of circulating CD44v6 mRNA transcripts may be common in healthy subjects[42]. The non-epithelial marker guanylyl cyclase C appears to have promising specificity[36], but further evaluation of its usefulness is awaited. RT PCR-based identification of circulating *p53* mutations has allowed the preoperative identification of circulating tumour cells in some cases of colorectal cancer. That these *p53* mutations are always identical to those found in the corresponding primary tumour provides additional support for the origin of these circulating cells[43].

Clinical significance

Molecular techniques have been applied to detect circulating tumour cells in a variety of solid tumours[13,53,54]. Results vary greatly from study to study[55], but most workers have concluded that there is an association between the presence of circulating tumour cells before operation and decreased survival[56,57]. Exploration of several different types of epithelial malignancy within a single study[15,21,25,34] limits conclusions for colorectal cancer. At present, the presence of circulating tumour cells cannot be considered a reliable prognostic indicator in any common solid malignancy owing to the absence of large standardized trials with sufficient follow-up[55,58].

Causes of disparate results

Variability in technical factors, such as timing and handling of samples, selection of primers and PCR product detection methods, makes it difficult to compare results from different studies[55]. Extreme sensitivity increases the risk of false positives, either from sample contamination[59] or the amplification of transcripts arising from illegitimate transcription (the ectopic or background expression of a gene transcript in a tissue where it would not usually be expressed[60,61]). Since RT PCR assays rely on identification of mRNA that transcribes epithelium-related proteins, the inclusion of venepuncture-cored skin epithelial cells within the blood sample may yield false-positive results[20]. Sampling blood from a preaspirated cannula reduces the false-positive rate to below 5 per cent[32,62], but only two studies included this important precaution[27,33]. The number of PCR cycles used is a significant predictor of a positive amplification result ($P = 0{\cdot}003$)[62], but the number of cycles used has varied from 29[32,25,41] to 105[24] (*Table 1*).

False-negative results may also occur. Varying detection thresholds between patients may be the result of intertumoral variation in mRNA expression[58]. Experimental studies suggest that circulating tumour cells are aggregated in clumps[63] and are not homogeneously distributed, causing sample to sample variation in the number of tumour cells present within different blood samples. Although multiple blood sampling increases the rate of circulating colorectal cancer cell detection[32], most studies tested single blood samples for just one mRNA marker[15,20–22,24–31] and so may have underestimated the prevalence of circulating tumour cells. Large, long-term clinical studies are now required, using standardized RT PCR assays with carefully defined protocols and quality control. These should permit

Table 3 Bone marrow immunocytochemical studies in colorectal cancer

Reference	Year	Marker	mAb	No. of patients	Patients with 'positive' bone marrow (%)	Median follow-up (months)	Prognostic effect of 'positivity'	No. of healthy controls	False positives (%)
Schlimok *et al.*[69]	1987	CK18	CK2	39	21	NA	NA	75	0
Schlimok *et al.*[70]	1990	CK18	CK2	156	27	26	'Adverse'	0	NA
Lindemann *et al.*[71]	1992	CK18	CK2	88	32	35	'Adverse'	102	0
Juhl *et al.*[72]	1994	CK	KL-1	58	29	NA	NA	0	NA
Litle *et al.*[73]	1997	CK20	Anti-CK20	18	89	NA	NA	12	60
Leinung *et al.*[74]	2000	CK	A45-B/B3	145	25	39 (mean)	'Adverse'	51	0

mAb, monoclonal antibody; CEA, carcinoembryonic antigen; CK, cytokeratin; NA, not assessed

the clinical significance of circulating tumour cells to be understood fully.

Bone marrow studies

Experimental evidence suggests that circulating tumour cells are cleared from the bloodstream within 24 h of primary colorectal cancer resection[64]. The problems of poor sensitivity relating to the detection of tumour cells in the circulation might be overcome by examining the bone marrow, where tumour cells might persist for longer periods.

Immunocytochemical detection of tumour cells in bone marrow

Immunocytochemical staining of epithelial cell markers should allow reliable differentiation of tumour cells from mesenchymal cells present in normal bone marrow. Cytokeratin filaments are expressed predominantly in epithelial tissues[65], even after malignant transformation, and are rarely detected in haemopoietic cells[66–68]. Using CK18 as a marker for bone marrow tumour cells[69–71], preoperative bone marrow positivity has varied between 21 and 32 per cent in colorectal cancer (*Table 3*). Schlimok *et al.*[69] were able to identify CK18-positive cells in the bone marrow of eight of 39 patients with colorectal cancer. In a later study by the same group[70], 42 (27 per cent) of 156 patients had CK18-positive cells in their bone marrow before operation, and this was associated with a significantly higher relapse rate than in patients with negative bone marrow. Unfortunately, median follow-up in this study was only 26 months and healthy controls were not included (*Table 3*). Although CK20 is expressed by over 95 per cent of colorectal adenocarcinomas and is the most tissue-specific cytokeratin[65], its use as an immunocytochemical marker in bone marrow has been confined to one small study[73].

Clinical significance

A recent meta-analysis concluded that the prognostic importance of bone marrow tumour cells in solid epithelial tumours required further substantiation[75]. While 14 of 20 studies correlated bone marrow tumour cells with reduced relapse-free survival by univariate analysis, only five of 11 confirmed that this was an independent predictor of reduced disease-free survival. Of the two colorectal cancer studies in this meta-analysis, both demonstrated a significant correlation between positive bone marrow status and relapse-free survival on univariate analysis[70,71] (*Table 3*).

Perhaps the most important publication to date has been that of Lindemann *et al.*[71]. Using an anti-CK18 stain, bone marrow status was found to be an independent predictor of disease-free survival on multivariate analysis ($P = 0{\cdot}0035$); over 100 healthy control patients were negative[71]. Bone marrow-positive patients had significantly shorter disease-free survival ($P = 0{\cdot}0084$), but the relatively small sample size of 88 patients and short median follow-up of 35 months limit the study's conclusions. Leinung *et al.*[74] recently reported similar results in 145 patients with colorectal cancer using the A45-B/B3 pan-cytokeratin antibody, suggesting the need for larger multi-institutional clinical trials using a standardized bone marrow staining method, as proposed by Pantel *et al.*[67,76].

Molecular detection of tumour cells in bone marrow

Several factors limit the usefulness of some markers as targets in molecular assays (*Table 2*). Evidence exists for the presence of CK18[48] and CK19[49] pseudogenes (non-functional DNA sequences showing a high degree of sequence homology to a functional gene). Pseudogenes are readily transcribed and may cause false-positive results. Furthermore, illegitimate transcription of CK8, CK18[46,47] and CK19[50] in normal bone marrow tissue renders these markers unsuitable for bone marrow tumour cell detection

Table 4 Bone marrow reverse transcriptase polymerase chain reaction studies in colorectal cancer

Reference	Year	Marker	PCR cycles	No. of patients	Patients with 'positive' bone marrow (%)	Median follow-up (months)	Prognostic effect of 'positivity'	No. of healthy controls	False positives (%)
Gerhard *et al.*[14]	1994	CEA	50	6	66	NA	NA	8	0
Soeth *et al.*[78]	1996	CK20	60	57	35	NA	NA	2	50
Gunn *et al.*[50]	1996	CK19	35	15 BMA	6 BMA	NA	NA	4	5 of 12 BMA
		CK20	40	15 BMA	0	NA	NA	4	0
Soeth *et al.*[21]	1997	CK20	60	65	31	NS	'Adverse'	0	NA
Weitz *et al.*[31]	1999	CK20	70	14	21	NA	NA	0	NA
Weitz *et al.*[40]	2000	CK20	70	30	27	NA	NA	NS	NS

PCR, polymerase chain reaction; CEA, carcinoembryonic antigen; CK, cytokeratin; BMA, bone marrow aspirate (number of patients not stated); NA, not assessed; NS, not stated

using RT PCR. A CK20 pseudogene has yet to be identified and most workers have found CK20 mRNA to be absent from normal bone marrow[19,50,77].

Six small studies using RT PCR to detect tumour cells in bone marrow were identified, the largest from Soeth *et al.*[78] (*Table 4*). In this study, 20 (35 per cent) of 57 patients with colorectal cancer had CK20 mRNA-positive bone marrow before primary tumour resection. CK20 positivity was directly related to tumour stage according to the UICC classification[79], with only one of 16 benign controls testing positive. In a later study, the presence of CK20 mRNA in bone marrow before operation was associated with shorter survival, but the independent predictive power was not fully established[21].

With only a single, small study identified[14], the suitability of CEA mRNA as a target marker in bone marrow cannot be regarded as established (*Table 4*). Although 56 control samples were negative in this study, others have found a high proportion of normal bone marrow aspirates to be CEA mRNA positive[47]. These differences may be due to variations in assay methodology or contamination by epithelial cells from skin or sweat glands, which are known to express CEA[20].

Clinical significance

Further large clinical studies are needed in the case of colorectal cancer, as it is not clear whether the presence of RT PCR-detected bone marrow tumour cells offers better prediction of response than that achieved by histological examination of lymph nodes.

Influence of tumour resection on occult disease status

Circulating mRNA transcripts have been detected with greater frequency following colorectal cancer surgery, prompting some researchers to conclude that surgical manipulation may release tumour cells into the circulation[15,27,37,39,40]. Animal studies suggest that cell shedding enhances the development of metastases[80], and this was the reason for development of the 'no-touch isolation technique' of colorectal cancer resection[81]. However, there is little evidence to support any clinical benefit using this approach[82]. Conversely, others have found that tumour cells often disappear from the circulation after primary resection. In one study, persisting CEA mRNA positivity was higher in patients with lymph node involvement or distant metastases than in node-negative patients, although this was not statistically significant ($P = 0{\cdot}1$)[29]. Using a CEA and CK20 RT PCR assay, Patel *et al.*[35,41] have found that clearance of circulating tumour cells 24 h after primary tumour resection is greatest in Dukes' A and B disease and may therefore indicate improved outcome. Flow cytometric studies suggest that persistence of CK18-positive cells in bone marrow at 6 months after resection is significantly associated with the development of clinical metastases[83,84].

Lymph node studies

Identification of lymph node metastases currently determines tumour stage and indicates the need for adjuvant chemotherapy. Several approaches have been used to increase accuracy in the assessment of lymph node involvement by tumour.

Immunohistochemical detection of tumour cells in lymph nodes

The presence and the number of histologically involved lymph nodes are both independent prognostic indicators of survival in colorectal cancer[85,86]. Several earlier studies concluded that lymph node immunohistochemistry did not increase detection of tumour cells in comparison with routine haematoxylin and eosin staining[87–90]. However, most authors have reported tumour cells in isolation or in clusters within lymph nodes that would be considered tumour free on routinely stained sections[91–100], suggesting

Table 5 Lymph node immunohistochemical studies in colorectal cancer

Reference	Year	Marker	mAb	No. of node-negative patients	No. of nodes per patient	Node sectioning	Patients 'positive' on IHC (%)	Increased detection of tumour cells	Median follow-up (months)	Effect of 'positivity' on prognosis
O'Brien *et al.*[87]	1981	CEA	Anti-CEA	10	15	Single	0	No	NA	NA
Makin *et al.*[88]	1989	CK8, CK18, CK19	CAM 5.2	10	8	Single	10	No	36	ND
Davidson *et al.*[89]	1990	CEA EMA	Anti-CEA Anti-EMA	28	5	Single	2	No	NA	NA
Cutait *et al.*[91]	1991	CEA CK	Anti-CEA AE1/AE3	46	13	Single	26	Yes	60	ND
Haboubi *et al.*[92]	1992	CK	CAM 5.2	25	6*	Multi	32	Yes	NA	NA
Nicholson *et al.*[90]	1994	CK	CAM 5.2	33	16	Single	0	No	NA	NA
Jeffers *et al.*[93]	1994	CK	AE1/AE3	77	7	Single	25	Yes	82	ND
Greenson *et al.*[94]	1994	CK TAG72	AE1/AE3 CC49	50 50	11	Single	28 76	Yes	60	'Adverse'
Cote *et al.*[95]	1996	CK TAG72	AE1 CAM 5.2 CC49	NS	3	Multi	25	Yes	NA	NA
Adell *et al.*[96]	1996	CK8, CK18, CK19	Anti-CK	100	4	Multi	39	Yes	49	ND
Broll *et al.*[97]	1997	CK1, CK2 EP4	AE1/AE3 BerEP4	32	NS	Multi	19	Yes	84	ND
Sasaki *et al.*[98]	1997	CK	CAM 5·2	19	19	Multi	25% of nodes	Yes	NS	'Adverse'
Oberg *et al.*[99]	1998	CK	CAM 5·2	147	3–4	Single	32	Yes	28	ND
Hitchcock *et al.*[100]	1999	CK	AE1/AE3 CAM 5.2	173	10	Multi	16	Yes	NA	NA

*Before fat clearance. Multi, multiple; IHC, immunohistochemistry; mAb, monoclonal antibody; CEA, carcinoembryonic antigen; CK, cytokeratin; EMA and EP4, epithelial membrane antigen; TAG72, tumour-associated glycoprotein; NS, not stated; NA, not assessed; ND, no difference

that conventional lymph node examination may underestimate the pre-sence of tumour cells. Subjectivity in interpreting routinely stained sections is well recognized[100]. The incidence of immunohistochemically detected tumour cells in apparently negative lymph nodes has been reported at between 25 and 39 per cent using cytokeratin staining (*Table 5*).

What is the prognostic significance of immunohistochemically detected tumour cells? Greenson *et al.*[94] concluded that the finding of such cells in Dukes' B resection specimens, singly or in small clusters of two to three, correlated with adverse prognosis. Tumour cells were identified in 6 per cent of pericolic lymph nodes taken from 14 of 50 patients with Dukes' B tumours. At 5 years after resection, six of these 14 patients had died from recurrence compared with only one of 36 who were CK negative. While immunohistochemistry increases the detection of tumour cells in lymph nodes, most studies have concluded that it yields no additional prognostic information and that immunohistochemically detected lymph node tumour cells, found singly or in clusters, do not correlate with poorer outcome (*Table 5*)[88,91,96,97,99]. Jeffers *et al.*[93] compared survival of patients whose lymph nodes contained single tumour cells with that of patients who had clusters, and found no difference ($P = 0.55$).

The effect on prognosis of the anatomical location of tumour cells within a lymph node does not seem to have been explored, although several reports describe tumour cells mostly within the subcapsular sinuses[91,93,99]. This suggests that not all such cells present within lymph nodes are clinically important, and that some are destined to be destroyed by host immune responses[93]. In addition, since involved nodes are removed at the time of 'curative' surgery, microscopic foci of tumour cells present in lymph nodes may be a less ominous finding than tumour cells present in blood or bone marrow after removal of the primary tumour. It should be remembered that 38 per cent of patients with conventionally identified lymph node involvement are cured by excision of the involved nodes[101].

Clinical significance

In the case of colorectal cancer, the clinical significance of immunohistochemically detected tumour cells present in excised lymph nodes remains unclear. However, in a recent multi-institutional study of 736 patients with breast cancer, the presence of immunohistochemically detected occult

Table 6 Lymph node reverse transcriptase polymerase chain reaction studies in colorectal cancer

Reference	Year	Marker	PCR cycles	No. of node-negative patients	No. of nodes per patient	Patient 'positive' on RT PCR (%)	Increased detection of tumour cells	Median follow-up (months)	Effect of node 'positivity' on prognosis	No. of healthy controls	False positives (%)
Mori *et al.*[77]	1995	CEA	40	1	7	100	Yes *versus* H&E	NA	NA	5	0
Gunn *et al.*[50]	1996	CK19	35	15	7	77% of nodes		NA	NA	8	85
		CK20	40	15	7	24% of nodes	Yes *versus* H&E	NA	NA	8	0
Wong *et al.*[22]	1997	CD44	60	6	NS	17	Yes	NA	NA	0	NA
Dorudi *et al.*[51]	1998	CK20	40	18	5–18	22	Yes *versus* IHC	1–13 (range)	NA	5	0
Futamura *et al.*[52]	1998	CEA and CK20	40	13	15	100	Yes	NA	NA	5	0
Ichikawa *et al.*[111]	1998	Matrilysin	30	60	4	3% of nodes	Yes	NA	NA	0	NA
Waldman *et al.*[112]	1998	GCC	70	7	3	29	Yes	NA	NA	0	NA
Mori *et al.*[25]	1998	CEA	50	NS	NS	40% all nodes	Yes	24	'Adverse'	8	0
Liefers *et al.*[113]	1998	CEA	35	26	7	54	Yes *versus* H&E/IHC	73	'Adverse'	2	—*
Weitz *et al.*[31]	1999	CK20	70	16	14	88	Yes	NA	NA	22	0
Merrie *et al.*[114]	1999	CK20	NS	66	NS	33	Yes	NA	NA	39	2·5
Bernini *et al.*[115]	2000	Mucin 2	35	43	8	28	Yes	NA	NA	3	0

*Positive at 40–45 cycles. PCR, polymerase chain reaction; RT, reverse transcriptase; CEA, carcinoembryonic antigen; CK, cytokeratin; GCC, guanylyl cyclase C; H&E, haemotoxylin and eosin; IHC, immunocytochemistry; NS, not stated; NA, not assessed

axillary lymph node metastases was found to be significant and, in the case of postmenopausal women, was an independent predictor of overall survival[102]. This reaffirms the need for larger studies with longer follow-up to establish the clinical significance of immunohistochemically detected tumour cells within lymph nodes in colorectal cancer.

The sentinel node

The sentinel lymph node, defined as the first node that receives lymph from the primary tumour, has the highest potential to contain tumour cells when they are present[103]. Examination of the sentinel lymph node has been used to increase the accuracy of nodal status predominantly in melanoma[103] and breast cancer[104], but the role of sentinel node biopsy in colorectal cancer is not at present well established. Unlike sentinel node biopsy in breast cancer, the aim is not to reduce the extent of lymphadenectomy, but rather to allow improved staging without the need for painstaking immunohistochemical analysis of all retrieved nodes. Saha *et al.*[105] showed that the sentinel lymph node could be identified successfully at operation in 85 (99 per cent) of 86 patients using blue dye. In 29 (34 per cent) of 85, sentinel nodes contained metastases. Interestingly, in 95 per cent of patients in whom the sentinel node was negative all non-sentinel nodes were also negative. When the sentinel node was negative, only five (0·4 per cent) of 1184 non-sentinel nodes contained 'micrometastases'. In seven patients, tumour cells were seen in only one or two of ten sections of a solitary sentinel lymph node and, of these, two were seen only on immunohistochemical examination, suggesting a possible role for sentinel lymph node biopsy with multiple sectioning and immunohistochemical staining to increase staging accuracy. The low incidence of skip lesions suggests that sentinel lymph node mapping may be accurate in predicting lymph node metastases, but follow-up studies are required to determine whether this approach improves the prediction of prognosis in colorectal cancer.

Molecular detection of tumour cells in lymph nodes

Polymerase chain reaction studies

Using a mutant allele-specific amplification (MASA) PCR technique, Hayashi *et al.*[106] were able to detect *p53* and K-*ras* mutations in the primary tumours of 71 (59 per cent) of 120 patients with Dukes' A and B tumours. Of these 71 patients, 37 (52 per cent) had the same *p53* or K-*ras* gene mutation present in lymph nodes and 27 patients in this group relapsed within 5 years of surgery, in contrast to none of the 34 patients who were lymph node MASA negative. However, in 49 (41 per cent) of 120 cases the primary tumour did not contain any somatic changes suitable for amplification by PCR, a similar finding to that of Thebo *et al.*[107] in a more recent, but smaller, study. There are no known mutations that occur consistently in colorectal neoplasms[108], and mutations of the K-*ras* or *p53* genes are present in only 38 per cent[109] and 70 per cent[110] of colorectal tumours respectively, limiting the usefulness of this approach.

Reverse transcriptase polymerase chain reaction studies

The use of RT PCR to detect tissue-specific mRNA in histologically negative lymph nodes increases tumour cell detection compared with either haematoxylin and eosin staining or immunocytochemistry[22,25,31,50–52,77,111–115] (*Table 6*). CK8, CK18 and CK19 are unsuitable as markers of occult tumour cells in lymph nodes (*Table 2*). CK20 is not expressed in normal lymph node tissue[31,50–52], but studies using this marker are distinguished by small numbers of patients[31,50–52], no follow-up[31,50,52] or both[116], limiting conclusions about outcome.

RT PCR has been used to detect CEA mRNA in surgically retrieved lymph nodes[25,52,77,113]. Liefers *et al.*[113] reported a significant reduction in 5-year adjusted survival in a study of 26 patients with colorectal tumours with histologically negative but CEA mRNA-positive lymph nodes ($P = 0{\cdot}02$, log rank test). Other markers have been used, but these are of uncertain value owing to small study size or lack of follow-up (*Table 6*). Wong *et al.*[22] used a RT PCR assay to detect tumour-specific CD44 variants in lymph nodes from colorectal cancer resection specimens. However, not all carcinomas express the variant containing exon v6 which may confer metastatic potential[117], and CD44v6 expression is absent altogether from some metastatic colorectal cancers[118], rendering CD44 unsuitable as a marker. Mucin 2[115], matrilysin[111] and guanylyl cyclase C[112] have all been used as markers to detect occult lymph node disease in single studies, but further evaluation and follow-up data are required to ascertain any advantage from their use.

Clinical significance

Molecular assays increase detection of occult tumour cells in lymph nodes, and the work of Hayashi *et al.*[106] and Liefers *et al.*[113] suggests that these might be clinically important. However, the prognostic value of molecular assays used in the context of colorectal cancer, and in other common solid epithelial malignancies, has yet to be fully confirmed in larger studies[58].

Discussion

Twenty-five years after Salsbury's review[8], tumour cells in blood, bone marrow and lymph node tissue can be detected with three orders of magnitude greater sensitivity. At present immunocytochemical assays remain the benchmark for detecting occult disease in bone marrow, with several studies suggesting an association between positive bone marrow status and poorer survival. The greater sensitivity of molecular assays suggests that these may have the potential to increase staging accuracy, particularly in identifying relatively infrequent tumour cells in the blood. Following primary cancer resection, tumour cells may disappear from the circulation[10,27,29,35,41] or bone marrow[83] and so the presence of occult tumour cells in blood or marrow before resection may not be an ominous sign. The term minimal residual disease should probably be used only when tumour cells are present in patients who have had the primary tumour resected, and in whom there is no clinical evidence of persisting disease[6].

Despite these advances in detection, the clinical significance of small numbers of colorectal tumour cells in blood, lymph nodes and bone marrow has yet to be fully understood. Interlaboratory differences in the techniques used and the absence of large studies correlating occult disease with clinical outcome are partially responsible for this uncertainty. In addition, some patients who undergo curative primary resection may have persistently detectable tumour cells without adverse clinical manifestations. A lack of understanding of tumour cell dormancy[119], the ability of disseminated cells to remain latent for long periods before tumour recurrence becomes clinically manifest, further impedes the evaluation of the clinical significance of occult tumour cell dissemination.

In conclusion, conventional staging methods for colorectal cancer are imprecise. The ability reliably to identify small numbers of tumour cells within a clinical sample after primary tumour removal challenges our understanding of the biological and clinical significance of persisting cancer cells. Treatment planning will be more rational when the significance of minimal residual disease is better understood.

Acknowledgements

G.T. was supported by Colon Cancer Concern, London, UK, and by the Chelsea and Westminster Hospital Research Trustees. H.P. was a Stefan Galeskie Research Fellow.

References

1 International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995; **345**: 939–44.

2 Dukes CE. The classification of cancer of the rectum. *J Pathol Bacteriol* 1932; **35:** 323–32.

3 Dukes CE, Bussey HJR. The spread of rectal cancer and its effect on prognosis. *Br J Cancer* 1958; **12:** 309–20.

4 International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol* 1999; **17:** 1356–63.

5 Huvos AG, Hutter RV, Berg JW. Significance of axillary macrometastases and micrometastases in mammary cancer. *Ann Surg* 1971; **173:** 44–6.

6 Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer* 1999; **86:** 2668–73.

7 Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312:** 1604–8.

8 Salsbury AJ. The significance of the circulating cancer cell. *Cancer Treat Rev* 1975; **2:** 55–72.

9 Leather AJ, Gallegos NC, Kocjan G, Savage F, Smales CS, Hu W *et al.* Detection and enumeration of circulating tumour cells in colorectal cancer. *Br J Surg* 1993; **80:** 777–80.

10 Krag DN, Ashkaga T, Moss TJ, Kusminsky RE, Feldman S, Carp NZ *et al.* Breast cancer cells in the blood: a pilot study. *The Breast Journal* 1999; **5:** 354–8.

11 Mullis K, Faloona F, Scharf S, Saiki R, Horn G, Erlich H. Specific enzymatic amplification of DNA *in vitro*: the polymerase chain reaction. *Cold Spring Harb Symp Quant Biol* 1986; **51:** 263–73.

12 Saiki RK, Bugawan TL, Horn GT, Mullis KB, Erlich HA. Analysis of enzymatically amplified beta-globin and HLA-DQ alpha DNA with allele-specific oligonucleotide probes. *Nature* 1986; **324:** 163–6.

13 Smith B, Selby P, Southgate J, Pittman K, Bradley C, Blair GE. Detection of melanoma cells in peripheral blood by means of reverse transcriptase and polymerase chain reaction. *Lancet* 1991; **338:** 1227–9.

14 Gerhard M, Juhl H, Kalthoff H, Schreiber HW, Wagener C, Neumaier M. Specific detection of carcinoembryonic antigen-expressing tumor cells in bone marrow aspirates by polymerase chain reaction. *J Clin Oncol* 1994; **12:** 725–9.

15 Mori M, Mimori K, Ueo H, Karimine N, Barnard GF, Sugimachi K *et al.* Molecular detection of circulating solid carcinoma cells in the peripheral blood: the concept of early systemic disease. *Int J Cancer* 1996; **68:** 739–43.

16 Hardingham JE, Kotasek D, Sage RE, Eaton MC, Pascoe VH, Dobrovic A. Detection of circulating tumor cells in colorectal cancer by immunobead-PCR is a sensitive prognostic marker for relapse of disease. *Mol Med* 1995; **1:** 789–94.

17 Leon SA, Shapiro B, Sklaroff DM, Yaros MJ. Free DNA in the serum of cancer patients and the effect of therapy. *Cancer Res* 1977; **37:** 646–50.

18 Kopreski MS, Benko FA, Kwee C, Leitzel KE, Eskander E, Lipton A *et al.* Detection of mutant K-*ras* DNA in plasma or serum of patients with colorectal cancer. *Br J Cancer* 1997; **76:** 1293–9.

19 Burchill SA, Bradbury MF, Pittman K, Southgate J, Smith B, Selby P. Detection of epithelial cancer cells in peripheral blood by reverse transcriptase–polymerase chain reaction. *Br J Cancer* 1995; **71:** 278–81.

20 Jonas S, Windeatt S, O-Boateng A, Fordy C, Allen-Mersh TG. Identification of carcinoembryonic antigen-producing cells circulating in the blood of patients with colorectal carcinoma by reverse transcriptase polymerase chain reaction. *Gut* 1996; **39:** 717–21.

21 Soeth E, Vogel I, Roder C, Juhl H, Marxsen J, Kruger U *et al.* Comparative analysis of bone marrow and venous blood isolates from gastrointestinal cancer patients for the detection of disseminated tumor cells using reverse transcription PCR. *Cancer Res* 1997; **57:** 3106–10.

22 Wong LS, Cantrill JE, Odogwu S, Morris AG, Fraser IA. Detection of circulating tumour cells and nodal metastasis by reverse transcriptase–polymerase chain reaction technique. *Br J Surg* 1997; **84:** 834–9.

23 Denis MG, Lipart C, Leborgne J, LeHur PA, Galmiche JP, Denis M *et al.* Detection of disseminated tumor cells in peripheral blood of colorectal cancer patients. *Int J Cancer* 1997; **74:** 540–4.

24 Funaki NO, Tanaka J, Itami A, Kasamatsu T, Ohshio G, Onodera H *et al.* Detection of colorectal carcinoma cells in circulating peripheral blood by reverse transcription–polymerase chain reaction targeting cytokeratin-20 mRNA. *Life Sci* 1997; **60:** 643–52.

25 Mori M, Mimori K, Ueo H, Tsuji K, Shiraishi T, Barnard GF *et al.* Clinical significance of molecular detection of carcinoma cells in lymph nodes and peripheral blood by reverse transcription–polymerase chain reaction in patients with gastrointestinal or breast carcinomas. *J Clin Oncol* 1998; **16:** 128–32.

26 Wyld DK, Selby P, Perren TJ, Jonas SK, Allen-Mersh TG, Wheeldon J *et al.* Detection of colorectal cancer cells in peripheral blood by reverse-transcriptase polymerase chain reaction for cytokeratin 20. *Int J Cancer* 1998; **79:** 288–93.

27 Weitz J, Kienle P, Lacroix J, Willeke F, Benner A, Lehnert T *et al.* Dissemination of tumor cells in patients undergoing surgery for colorectal cancer. *Clin Cancer Res* 1998; **4:** 343–8.

28 Funaki NO, Tanaka J, Ohshio G, Onodera H, Maetani S, Imamura M. Cytokeratin 20 mRNA in peripheral venous blood of colorectal carcinoma patients. *Br J Cancer* 1998; **77:** 1327–32.

29 Castells A, Boix L, Bessa X, Gargallo L, Pique JM. Detection of colonic cells in peripheral blood of colorectal cancer patients by means of reverse transcriptase and polymerase chain reaction. *Br J Cancer* 1998; **78:** 1368–72.

30 Champelovier P, Mongelard F, Seigneurin D. CK20 gene expression: technical limits for the detection of circulating tumor cells. *Anticancer Res* 1999; **19:** 2073–8.

31 Weitz J, Kienle P, Magener A, Koch M, Schrodel A, Willeke F *et al.* Detection of disseminated colorectal cancer cells in

lymph nodes, blood and bone marrow. *Clin Cancer Res* 1999; 5: 1830–6.

32 Wharton RQ, Jonas SK, Glover C, Khan ZA, Klokouzas A, Quinn H *et al.* Increased detection of circulating tumor cells in the blood of colorectal carcinoma patients using two reverse transcription-PCR assays and multiple blood samples. *Clin Cancer Res* 1999; 5: 4158–63.

33 Jung R, Petersen K, Kruger W, Wolf M, Wagener C, Zander A *et al.* Detection of micrometastasis by cytokeratin 20 RT–PCR is limited due to stable background transcription in granulocytes. *Br J Cancer* 1999; 81: 870–3.

34 Noh YH, Im G, Ku JH, Lee YS, Ahn MJ. Detection of tumor cell contamination in peripheral blood by RT-PCR in gastrointestinal cancer patients. *J Korean Med Sci* 1999; 14: 623–8

35 Patel H, Le-Marer N, Wharton R, Khan ZAJ, Araia R, Allen-Mersh TG. Clearance of circulating tumour cells from the circulation after primary colorectal cancer removal may indicate improved outcome. *Eur J Surg Oncol* 1999; 25: 650 (Abstract).

36 Bustin SA, Gyselman VG, Williams NS, Dorudi S. Detection of cytokeratins 19/20 and guanylyl cyclase C in peripheral blood of colorectal cancer patients. *Br J Cancer* 1999; 79: 1813–20.

37 Funaki NO, Tanaka J, Sugiyama T, Ohshio G, Nonaka A, Yotsumoto F *et al.* Perioperative quantitative analysis of cytokeratin 20 mRNA in peripheral venous blood of patients with colorectal adenocarcinoma. *Oncol Rep* 2000; 7: 271–6.

38 Hardingham JE, Hewett PJ, Sage RE, Finch JL, Nuttall JD, Kotasek D *et al.* Molecular detection of blood-borne epithelial cells in colorectal cancer patients and in patients with benign bowel disease. *Int J Cancer* 2000; 89: 8–13.

39 Yamaguchi K, Takagi Y, Aoki S, Futamura M, Saji S. Significant detection of circulating cancer cells in the blood by reverse transcriptase–polymerase chain reaction during colorectal cancer resection. *Ann Surg* 2000; 232: 58–65.

40 Weitz J, Koch M, Kienle P, Schrodel A, Willeke F, Benner A *et al* Detection of hematogenic tumor cell dissemination in patients undergoing resection of liver metastases of colorectal cancer. *Ann Surg* 2000; 232: 66–72.

41 Patel H, Le-Marer N, Wharton RQ, Khan ZAJ, Araia R, Henry MM *et al* Clearance of circulating tumour cells in colorectal cancer is greatest in tumours with the best prognosis. *Br J Surg* 2000, 87: 630 (Abstract).

42 Masson D, Denis MG, Lustenberger P. Limitations of CD44v6 amplification for the detection of tumour cells in the blood of colorectal cancer patients. *Br J Cancer* 2000; 82: 1283–9.

43 Khan ZAJ, Jonas SK, Le-Marer N, Patel H, Wharton RQ, Tarragona A *et al. P53* mutations in primary and metastatic tumors and circulating tumor cells from colorectal carcinoma patients. *Clin Cancer Res* 2000; 6: 3499–504.

44 Taniguchi T, Makino M, Suzuki K, Kaibara N. Prognostic significance of reverse transcriptase–polymerase chain reaction measurement of carcinoembryonic antigen mRNA levels in tumor drainage blood and peripheral blood of patients with colorectal carcinoma. *Cancer* 2000; 89: 970–6.

45 Nakamori S, Kameyama M, Furukawa H, Takeda O, Sugai S, Imaoka S *et al.* Genetic detection of colorectal cancer cells in circulation and lymph nodes. *Dis Colon Rectum* 1997; 40(Suppl 10): S29–36.

46 Traweek ST, Liu J, Battifora H. Keratin gene expression in non-epithelial tissues. Detection with polymerase chain reaction. *Am J Pathol* 1993, 142: 1111–18.

47 Zippelius A, Kufer P, Honold G, Kollermann MW, Oberneder R, Schlimok G *et al.* Limitations of reverse-transcriptase polymerase chain reaction analyses for detection of micrometastatic epithelial cancer cells in bone marrow. *J Clin Oncol* 1997; 15: 2701–8.

48 Neumaier M, Gerhard M, Wagener C. Diagnosis of micrometastases by the amplification of tissue-specific genes. *Gene* 1995; 159: 43–7.

49 Ruud P, Fodstad O, Hovig E. Identification of a novel cytokeratin 19 pseudogene that may interfere with reverse transcriptase–polymerase chain reaction assays used to detect micrometastatic tumor cells. *Int J Cancer* 1999; 80: 119–25.

50 Gunn J, McCall JL, Yun K, Wright PA. Detection of micrometastases in colorectal cancer patients by K19 and K20 reverse-transcription polymerase chain reaction. *Lab Invest* 1996; 75: 611–16.

51 Dorudi S, Kinrade E, Marshall NC, Feakins R, Williams NS, Bustin SA. Genetic detection of lymph node micrometastases in patients with colorectal cancer. *Br J Surg* 1998; 85: 98–100.

52 Futamura M, Takagi Y, Koumura H, Kida H, Tanemura H, Shimokawa K *et al* Spread of colorectal cancer micrometastases in regional lymph nodes by reverse transcriptase–polymerase chain reactions for carcinoembryonic antigen and cytokeratin 20. *J Surg Oncol* 1998; 68: 34–40.

53 Israeli RS, Miller WH Jr, Su SL, Powell CT, Fair WR, Samadi DS *et al.* Sensitive nested reverse transcription polymerase chain reaction detection of circulating prostatic tumor cells. comparison of prostate-specific membrane antigen and prostate-specific antigen-based assays. *Cancer Res* 1994; 54: 6306–10.

54 Datta YH, Adams PT, Drobyski WR, Ethier SP, Terry VH, Roth MS. Sensitive detection of occult breast cancer by the reverse-transcriptase polymerase chain reaction. *J Clin Oncol* 1994, 12: 475–82.

55 Zippelius A, Pantel K. RT-PCR-based detection of occult disseminated tumor cells in peripheral blood and bone marrow of patients with solid tumors. An overview. *Ann N Y Acad Sci* 2000; 906: 110–23.

56 Olsson CA, de Vries GM, Raffo AJ, Benson MC, O'Toole K, Cao Y *et al.* Preoperative reverse transcriptase polymerase chain reaction for prostate specific antigen predicts treatment failure following radical prostatectomy. *J Urol* 1996; 155: 1557–62.

57 Ghossein RA, Coit D, Brennan M, Zhang ZF, Wang Y, Bhattacharya S *et al.* Prognostic significance of peripheral blood and bone marrow tyrosinase messenger RNA in malignant melanoma *Clin Cancer Res* 1998; 4: 419–28.

58 Ghossein RA, Bhattacharya S, Rosai J. Molecular detection of micrometastases and circulating tumor cells in solid tumors. *Clin Cancer Res* 1999; **5:** 1950–60.

59 Keilholz U, Willhauck M, Rimoldi D, Brasseur F, Dummer W, Rass K *et al.* Reliability of reverse transcription–polymerase chain reaction (RT-PCR)-based assays for the detection of circulating tumour cells: a quality-assurance initiative of the EORTC Melanoma Cooperative Group. *Eur J Cancer* 1998; **34:** 750–3.

60 Chelly J, Kaplan JC, Maire P, Gautron S, Kahn A. Transcription of the dystrophin gene in human muscle and non-muscle tissue. *Nature* 1988; **333:** 858–60.

61 Kaplan JC, Kahn A, Chelly J. Illegitimate transcription: its use in the study of inherited disease. *Hum Mutat* 1992; **1:** 357–60.

62 Wharton RQ, Jonas SK, Stupnicka C, Weston M, Allen-Mersh T. Elimination of false positives in RT-PCR used to detect circulating tumour cells in colorectal cancer. *Gut* 1997; **42**(Suppl 1): A91 (Abstract).

63 Liotta LA, Kleinerman J, Saidel GM. Quantitative relationships of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Res* 1974; **34:** 997–1004.

64 Fidler IJ. Metastasis: quantitative analysis of distribution and fate of tumor emboli labeled with ^{125}I-5-iodo-2′-deoxy-uridine. *J Natl Cancer Inst* 1970; **45:** 773–82.

65 Moll R, Franke WW, Schiller DL, Geiger B, Krepler R. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. *Cell* 1982; **31:** 11–24.

66 Pantel K, Izbicki J, Passlick B, Angstwurm M, Haussinger K, Thetter O *et al.* Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. *Lancet* 1996; **347:** 649–53.

67 Pantel K, Schlimok G, Angstwurm M, Weckermann D, Schmaus W, Gath H *et al.* Methodological analysis of immunocytochemical screening for disseminated epithelial tumor cells in bone marrow. *J Hematother* 1994; **3:** 165–73.

68 Braun S, Muller M, Hepp F, Schlimok G, Riethmuller G, Pantel K. Re: Micrometastatic breast cancer cells in bone marrow at primary surgery: prognostic value in comparison with nodal status. *J Natl Cancer Inst* 1998; **90:** 1099–101 (Letter).

69 Schlimok G, Funke I, Holzmann B, Gottlinger G, Schmidt G, Hauser H *et al.* Micrometastatic cancer cells in bone marrow: *in vitro* detection with anti-cytokeratin and *in vivo* labeling with anti-17-1A monoclonal antibodies. *Proc Natl Acad Sci USA* 1987; **84:** 8672–6.

70 Schlimok G, Funke I, Bock B, Schweiberer B, Witte J, Riethmuller G. Epithelial tumor cells in bone marrow of patients with colorectal cancer: immunocytochemical detection, phenotypic characterization, and prognostic significance. *J Clin Oncol* 1990; **8:** 831–7.

71 Lindemann F, Schlimok G, Dirschedl P, Witte J, Riethmuller G. Prognostic significance of micrometastatic tumour cells in bone marrow of colorectal cancer patients. *Lancet* 1992; **340:** 685–9.

72 Juhl H, Stritzel M, Wroblewski A, Henne Bruns D, Kremer D, Schmiegel W *et al.* Immunocytological detection of micrometastatic cells: comparative evaluation of findings in the peritoneal cavity and the bone marrow of gastric, colorectal and pancreatic cancer patients. *Int J Cancer* 1994; **57:** 330–5.

73 Litle VR, Warren RS, Moore D II, Pallavicini MG. Molecular cytogenetic analysis of cytokeratin 20-labeled cells in primary tumors and bone marrow aspirates from colorectal carcinoma patients. *Cancer* 1997; **79:** 1664–70.

74 Leinung S, Wurl P, Weiss CL, Roder I, Schonfelder M. Cytokeratin-positive cells in bone marrow in comparison with other prognostic factors in colon carcinoma. *Langenbecks Arch Surg* 2000; **385:** 337–43.

75 Funke I, Schraut W. Meta-analyses of studies on bone marrow micrometastases: an independent prognostic impact remains to be substantiated. *J Clin Oncol* 1998; **16:** 557–66.

76 Braun S, Pantel K. Immunodiagnosis and immunotherapy of isolated tumor cells disseminated to bone marrow of patients with colorectal cancer. *Tumori* 1995; **81**(Suppl 3): 78–83.

77 Mori M, Mimori K, Inoue H, Barnard GF, Tsuji K, Nanbara S *et al.* Detection of cancer micrometastases in lymph nodes by reverse transcriptase–polymerase chain reaction. *Cancer Res* 1995; **55:** 3417–20.

78 Soeth E, Roder C, Juhl H, Kruger U, Kremer B, Kalthoff H. The detection of disseminated tumor cells in bone marrow from colorectal-cancer patients by a cytokeratin-20-specific nested reverse-transcriptase–polymerase-chain reaction is related to the stage of disease. *Int J Cancer* 1996; **69:** 278–82.

79 Hermanek P, Scheibe O, Spiessl B, Wagner G. TNM classification of malignant tumors: new 1987 edition. *Langenbecks Arch Chir* 1987; 371: 1–2.

80 Nishizaki T, Matsumata T, Kanematsu T, Yasunaga C, Sugimachi K. Surgical manipulation of VX2 carcinoma in the rabbit liver evokes enhancement of metastasis. *J Surg Res* 1990; **49:** 92–7.

81 Turnbull RB Jr, Kyle K, Watson FR, Spratt J. Cancer of the colon: the influence of the no-touch isolation technic on survival rates. *Ann Surg* 1967; **166:** 420–7.

82 Wiggers T, Jeekel J, Arends JW, Brinkhorst AP, Kluck HM, Luyk CI *et al.* No-touch isolation technique in colon cancer: a controlled prospective trial. *Br J Surg* 1988; **75:** 409–15.

83 O'Sullivan GC, Collins JK, Kelly J, Morgan J, Madden M, Shanahan F. Micrometastases: marker of metastatic potential or evidence of residual disease? *Gut* 1997; **40:** 512–15.

84 O'Sullivan GC, Collins JK, O'Brien F, Crowley B, Murphy K, Lee G *et al.* Micrometastases in bone marrow of patients undergoing 'curative' surgery for gastrointestinal cancer. *Gastroenterology* 1995; **109:** 1535–40.

85 Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Large bowel cancer: surgical pathology and its relationship to survival. *Br J Surg* 1984; **71:** 604–10.

86 Fielding LP, Phillips RK, Fry JS, Hittinger R. Prediction of outcome after curative resection for large bowel cancer. *Lancet* 1986; **ii:** 904–7.

87 O'Brien MJ, Zamcheck N, Burke B, Kirkham SE, Saravis CA, Gottlieb LS. Immunocytochemical localization of carcinoembryonic antigen in benign and malignant colorectal tissues. Assessment of diagnostic value. *Am J Clin Pathol* 1981; **75:** 283–90.

88 Makin CA, Bobrow LG, Nicholls RJ. Can immunohistology improve detection of lymph-node metastases in large-bowel cancer? *Dis Colon Rectum* 1989; **32:** 99–102.

89 Davidson BR, Sams VR, Styles J, Deane C, Boulos PB. Detection of occult nodal metastases in patients with colorectal carcinoma. *Cancer* 1990; **65:** 967–70.

90 Nicholson AG, Marks CG, Cook MG. Effect on lymph node status of triple levelling and immunohistochemistry with CAM 5.2 on node negative colorectal carcinomas. *Gut* 1994; **35:** 1447–8.

91 Cutait R, Alves VA, Lopes LC, Cutait DE, Borges JL, Singer J *et al.* Restaging of colorectal cancer based on the identification of lymph node micrometastases through immunoperoxidase staining of CEA and cytokeratins. *Dis Colon Rectum* 1991, **34:** 917–20.

92 Haboubi NY, Clark P, Kaftan SM, Schofield PF. The importance of combining xylene clearance and immunohistochemistry in the accurate staging of colorectal carcinoma. *J R Soc Med* 1992; **85:** 386–8.

93 Jeffers MD, O'Dowd GM, Mulcahy H, Stagg M, O'Donoghue DP, Toner M. The prognostic significance of immunohistochemically detected lymph node micrometastases in colorectal carcinoma. *J Pathol* 1994; **172:** 183–7.

94 Greenson JK, Isenhart CE, Rice R, Mojzisik C, Houchens D, Martin EW Jr. Identification of occult micrometastases in pericolic lymph nodes of Dukes' B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. Correlation with long-term survival. *Cancer* 1994; **73:** 563–9.

95 Cote RJ, Houchens DP, Hitchcock CL, Saad AD, Nines RG, Greenson JK *et al.* Intraoperative detection of occult colon cancer micrometastases using ^{125}I-radiolabeled monoclonal antibody CC49. *Cancer* 1996; **77:** 613–20.

96 Adell G, Boeryd B, Franlund B, Sjodahl R, Hakansson L. Occurrence and prognostic importance of micrometastases in regional lymph nodes in Dukes' B colorectal carcinoma: an immunohistochemical study. *Eur J Surg* 1996; **162:** 637–42.

97 Broll R, Schauer V, Schimmelpenning H, Strik M, Woltmann A, Best R *et al.* Prognostic relevance of occult tumor cells in lymph nodes of colorectal carcinomas: an immunohistochemical study. *Dis Colon Rectum* 1997; **40:** 1465–71.

98 Sasaki M, Watanabe H, Jass JR, Ajioka Y, Kobayashi M, Matsuda K *et al.* Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in 'node-negative' colorectal cancer. *J Gastroenterol* 1997; **32:** 758–64.

99 Oberg A, Stenling R, Tavelin B, Lindmark G. Are lymph node micrometastases of any clinical significance in Dukes stages A and B colorectal cancer? *Dis Colon Rectum* 1998; **41:** 1244–9.

100 Hitchcock CL, Sampsel J, Young DC, Martin EW Jr, Arnold MW. Limitations with light microscopy in the detection of colorectal cancer cells. *Dis Colon Rectum* 1999; **42:** 1046–52.

101 NHS Executive. *Improving Outcomes in Colorectal Cancer. Guidance on Commissioning Cancer Services The Manual* London: Department of Health, 1997.

102 Cote RJ, Peterson HF, Chaiwun B, Gelber RD, Goldhirsch A, Castiglione-Gertsch M *et al.* Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. *Lancet* 1999; **354:** 896–900.

103 Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127:** 392–9.

104 Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C *et al.* The sentinel node in breast cancer – a multicenter validation study. *N Engl J Med* 1998; **339:** 941–6.

105 Saha S, Wiese D, Badin J, Beutler T, Nora D, Ganatra BK *et al.* Technical details of sentinel lymph node mapping in colorectal cancer and its impact on staging. *Ann Surg Oncol* 2000; **7:** 120–4.

106 Hayashi N, Ito I, Yanagisawa A, Kato Y, Nakamori S, Imaoka S *et al.* Genetic diagnosis of lymph-node metastasis in colorectal cancer. *Lancet* 1995; **345:** 1257–9.

107 Thebo JS, Senagore AJ, Reinhold DS, Stapleton SR. Molecular staging of colorectal cancer: K-*ras* mutation analysis of lymph nodes upstages Dukes B patients. *Dis Colon Rectum* 2000; **43:** 155–9 (Discussion 159–62).

108 Cawkell L, Quirke P. *The Molecular Biology and Genetics of Colorectal Cancer.* New York: Churchill Livingstone, 1996.

109 Andreyev HJ, Norman AR, Cunningham D, Oates JR, Clarke PA. Kirsten *ras* mutations in patients with colorectal cancer: the multicenter 'RASCAL' study. *J Natl Cancer Inst* 1998; **90:** 675–84.

110 Nigro JM, Baker SJ, Preisinger AC, Jessup JM, Hostetter R, Cleary K *et al.* Mutations in the *p53* gene occur in diverse human tumour types. *Nature* 1989; **342:** 705–8.

111 Ichikawa Y, Ishikawa T, Momiyama N, Yamaguchi S, Masui H, Hasegawa S *et al.* Detection of regional lymph node metastases in colon cancer by using RT-PCR for matrix metalloproteinase 7, matrilysin. *Clin Exp Metastasis* 1998; **16:** 3–8.

112 Waldman SA, Cagir B, Rakinic J, Fry RD, Goldstein SD, Isenberg G *et al.* Use of guanylyl cyclase C for detecting micrometastases in lymph nodes of patients with colon cancer. *Dis Colon Rectum* 1998; **41:** 310–15.

113 Liefers GJ, Cleton-Jansen AM, van de Velde CJ, Hermans J, van Krieken JH, Cornelisse CJ *et al.* Micrometastases and survival in stage II colorectal cancer. *N Engl J Med* 1998; **339:** 223–8

114 Merrie AE, Yun K, van Rij AM, McCall JL. Detection and significance of minimal residual disease in colorectal cancer. *Histol Histopathol* 1999; **14:** 561–9.

115 Bernini A, Spencer M, Frizelle S, Madoff RD, Willmott LD, McCormick SR *et al.* Evidence for colorectal cancer micrometastases using reverse transcriptase–polymerase chain reaction analysis of MUC2 in lymph nodes. *Cancer Detect Prev* 2000; **24:** 72–9.
116 Merrie AEH, Gunn J, Phillips LV, McCall JL, Yun K. Prognostic significance of colorectal cancer micrometastases detected by reverse transcription polymerase chain recation (RT-PCR). *Gut* 1998; **42**(Suppl 1): A90 (Abstract).
117 Wielenga VJ, Heider KH, Offerhaus GJ, Adolf GR, van den Berg FM, Ponta H *et al.* Expression of CD44 variant proteins in human colorectal cancer is related to tumor progression. *Cancer Res* 1993; **53:** 4754–6.
118 Gotley DC, Fawcett J, Walsh MD, Reeder JA, Simmons DL, Antalis TM. Alternatively spliced variants of the cell adhesion molecule CD44 and tumour progression in colorectal cancer. *Br J Cancer* 1996; **74:** 342–51.
119 Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med* 1995; **1:** 149–53.

Randomized clinical trial comparing suture and mesh repair of umbilical hernia in adults

A. Arroyo, P. García, F. Pérez, J. Andreu, F. Candela and R. Calpena

Ambulatory Surgery Unit, Department of Surgery, University Hospital of Elche, Elche, Spain
Correspondence to: Dr A. Arroyo, Avenida Oscar Esplá 35 E4-6°D, CP 03007, Alicante, Spain (e-mail: arroyocir@hotmail.com)

Background: Prosthetic repair has become the standard method for inguinal hernia and has excellent results. The question remains of whether the mesh technique could also improve results for umbilical defects.

Methods: The study was a randomized clinical trial comparing herniorrhaphy (primary suture) with hernioplasty (polypropylene mesh or plug) in 200 adult patients with a primary umbilical hernia. Patients at high anaesthetic risk (American Society of Anesthesiologists (ASA) grade IV) or those who needed emergency surgery were excluded. The mean postoperative follow-up was 64 months. The population studied included 118 women and 82 men with a mean age at presentation of 57 years. Some 173 patients were ASA grade I–II and 27 were ASA III. The anaesthetic technique of choice was local anaesthetic infiltration plus sedation (98 per cent).

Results: There were no significant anaesthetic complications or surgical deaths. The mean duration of surgery was greater for mesh than for suture repair (45 *versus* 38 min). Rates of early complications such as seroma, haematoma or wound infection were similar in the two groups. The hernia recurrence rate was higher after suture repair (11 per cent) than after mesh repair (1 per cent) ($P = 0{\cdot}0015$).

Conclusion: Prosthetic repair could become the standard treatment for primary umbilical hernia in adults.

Paper accepted 9 June 2001

British Journal of Surgery 2001, 88, 1321–1323

Introduction

Umbilical hernia is common in adults, but it has received little attention in comparison to other types of hernia of the abdominal wall[1]. The classical methods for repair of a midline hernia have resulted in high rates of recurrence[1]. The widespread use of mesh material in the treatment of inguinal, femoral and incisional hernias, with excellent low recurrence rates, has led to an evaluation of its use for umbilical hernias[2,3].

The present study compared suture and mesh repairs in an attempt to establish a standard technique for the treatment of primary umbilical hernia in adults.

Patients and methods

The study was a randomized study of 200 consecutive patients diagnosed with a primary umbilical hernia, who had elective repair at University General Hospital of Elche, from June 1992 to January 1998. The surgical option for each patient was selected at random as either a prosthetic (mesh) or non-prosthetic (suture) repair. Patients were allocated regardless of the hernia size using a computer randomization program. Fifteen other patients did not agree to enter the trial because they preferred prosthetic repair. Patients with significant anaesthetic risk (American Society of Anesthesiologists (ASA) grade IV) and those who needed emergency surgery were also excluded from the study.

The population studied included 118 women and 82 men, with mean age at presentation of 57 (range 14–79) years. Some 173 patients were ASA I–II and 27 patients were ASA III. The clinical characteristics and associated risk factors were similar in the two groups (*Table 1*). The majority of patients (195; 98 per cent) had surgery under local anaesthesia plus sedation, while general anaesthetic was administered for the remaining operations.

Table 1 Characteristics of patients undergoing umbilical hernia repair either with sutures or mesh

	Sutures (n = 100)	Mesh (n = 100)
Mean age (years)	56	57
Gender ratio (F : M)	60 : 40	58 : 42
ASA grade		
I–II	85	88
III	15	12
Hernia defect		
> 3 cm	30	32
< 3 cm	70	68
Anaesthesia		
Local	98	97
General	2	3
Mean duration of surgery (min)	38	45
Overnight stay in hospital	2	1

ASA, American Society of Anesthesiologists. There were no significant differences between groups

Surgical technique

A paraumbilical incision was made in both operative groups and the sac was dissected, avoiding resection. Both the sac and its content were restored into the abdominal cavity.

Herniorrhaphy was carried out in 100 patients using simple interrupted suture of the defect using non-absorbable polyester material (2 Ethibond; Ethicon, Edinburgh, UK). Hernioplasty was done in a second group of 100 patients using a polypropylene prosthesis placed in the extraperitoneal plane and fixed with individual sutures (0/0 Prolene; Ethicon). A mesh plug repair was used to repair defects up to 3 cm in diameter, whereas a mesh sheet was inserted for larger hernias. Patients had surgery done by a variety of surgeons with specialized training in hernia repair attached to the hospital's Abdominal Wall Unit.

All patients received a single intravenous dose of amoxicillin–clavulanic acid 2 g. After the operation, patients remained in the day surgery unit (DSU) for up to 6 h and were then discharged home. A longer stay was considered as an unplanned delay in discharge. Decisions regarding the anaesthetic and surgical options were left to the physician in charge.

After discharge, the home care unit, specially trained in postoperative care, followed the patients' recovery until skin staples were removed. Any complications were reported and treated, and patients were returned to hospital if necessary. On discharge, patients received a combination of oral analgesics (diclofenac 50 mg three times daily and paracetamol 1 g twice daily). Patient satisfaction with their postoperative analgesia was determined using a questionnaire (excellent, good, fair). Patients were followed up in the outpatient clinic by the same surgeons within the first month, and then annually.

Table 2 Complications after umbilical hernia repair

	Sutures (n = 100)	Mesh (n = 100)
Seroma	5	6
Haematoma	1	1
Wound infection	3	2
Other	2	1
Recurrence	11	1*

*P = 0·0015 *versus* sutures (χ^2 test with Yates' correction)

Data were collected from the patients' medical records for analysis, including the type of hernia, surgical procedure and anaesthetic techniques used, length of stay, and short- and long-term complications. Likewise, hernia recurrence was reported; recurrence was defined as the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed previously.

χ^2 test with Yates' correction was used to compare gender, anaesthesic risk and postoperative complications between groups. Student's t test was used to compare age and duration of surgery. $P < 0{\cdot}05$ was regarded as significant for both tests. Analysis of variance was used to compare variables between the groups.

Results

There were no significant anaesthetic complications or surgical deaths. The mean duration of surgery was greater for mesh than suture repair (45 *versus* 38 min), but the difference was not statistically significant. The mean postoperative stay in the DSU was 172 (range 105–300) min, and was similar in both groups. Two patients remained in hospital until the following day after suture repair and one after mesh repair although this was the result of anaesthesic advice rather than any surgical complication.

Among patients having suture repair, 30 had a hernia defect greater than 3 cm in diameter; the remainder were less than 3 cm. In the prosthesis group, the hernia defect was greater than 3 cm in 32 patients, all of whom had mesh repair. Sixty-eight patients underwent a mesh plug repair for a hernia defect smaller than 3 cm.

There was no significant difference in mean pain scores between the groups: 95 patients after mesh repair and 90 after suture repair graded the postoperative analgesia as excellent or good. Only five and ten patients in these groups respectively used additional analgesia. The rate of early postoperative complications such as seroma, haematoma or wound infection was similar after both procedures (*Table 2*).

The mean follow-up was 64 (range 21–80) months. There were no readmissions, systemic complications or deaths during follow-up in either group. The hernia recurrence rate was higher after suture repair (11 per cent) than after prosthetic repair (1 per cent) ($P = 0.0015$). There did not appear to be a significant relationship between recurrence rate and size of the hernia. Overall recurrence rates were similar for defects greater and smaller than 3 cm diameter: 8 *versus* 5 per cent respectively.

Discussion

Umbilical hernia in adults is relatively common and is characterized as being an acquired defect in over 90 per cent[1,4,5]. It is seen mainly in obese women, often after multiparity and in patients with cirrhosis. It is most likely to occur in the fifth and sixth decades of life[6,7].

Many surgical techniques have been described since Cheselden reported the first method for repair of an umbilical hernia in 1740[5]. In the last century, herniorrhaphy using simple suture[8] or Mayo's technique[9] was the most frequently used repair in specialized hernia centres. However, many retrospective studies have shown high recurrence rates (10–30 per cent), which have been taken for granted since there were no alternative treatments[1,5].

Hernia recurrence rates have been reduced to 1 per cent after incorporation of mesh material in the inguinal region, and this has become the treatment of choice[3]. Similar good results have been described for umbilical hernias[10,11].

The present study supports this tendency to favour hernioplasty for an umbilical hernia, since the rate of recurrence is clearly lower after mesh repair (1 per cent), regardless of hernia size. The associated morbidity (infection, seroma, haematoma) was not increased over that of suture repair. The fact that the repair is tension free might account for these results, as has been suggested for groin hernia repair[2].

Local anaesthetic and sedation was used as the technique of choice for umbilical hernia repair, as it has the lowest rate of systemic complications without any increase in recurrence or local complication rates[12]. Some studies have reported a beneficial effect of a single preoperative dose of antibiotic on wound infection rates[13], although this issue remains controversial. Finally, it is possible to perform the surgery as a day-case procedure, with ensuing social and economic advantages[14].

References

1 Hidalgo M, Higuero F, Álvarez-Caperochipi J, Machuca J, Laporte E, Figueroa J *et al.* Hernias de la pared abdominal. Estudio multicéntrico epidemiológico (1993–1994). *Cirugia Española* 1996; **59:** 309–405.

2 Rutkow MI, Robbins AW. Mesh plug hernia repair: a follow-up report. *Surgery* 1995; **117:** 597–8.

3 Lichtenstein IL, Shulman AG, Amid PK, Montllor MM. The tension-free hernioplasty. *Am J Surg* 1989; **157:** 188–93.

4 Morgan WW, White JJ, Stumbaugh S, Haller JA. Prophylactic umbilical hernia repair in childhood to prevent adult incarceration. *Surg Clin North Am* 1970; **50:** 839–45.

5 García Ureña MA, Rico Selas P, Seoane J, Marcello M, Moreno González E, Corral Sánchez MA *et al.* Hernia umbilical del adulto. Resultados a largo plazo en pacientes operados de urgencia. *Cirugia Española* 1994; **56:** 302–6.

6 Pescovitz MD. Umbilical hernia repair in patients with cirrhosis. No evidence for increased incidence of variceal bleeding. *Ann Surg* 1984; **199:** 325–7.

7 Harmel RP. Umbilical hernia. In: Nyhus LM, Condon RE, eds. *Hernia.* 3rd ed. Philadelphia, Pennsylvania: JB Lippincott, 1989: 347–52.

8 Farris JM, Smith GK, Beattie AS. Umbilical hernia: an inquiry into the principle of imbrication and a note on the preservation of the umbilical dimple. *Am J Surg* 1959; **98:** 236–42.

9 Mayo WJ. An operation for the radical cure of umbilical hernia. *Ann Surg* 1901; **34:** 276–80.

10 Amid PK, Shulman AG, Lichtenstein IL. Tension-free repair of umbilical, epigastric, and incisional hernias. *Contemp Surg* 1994; **44:** 177–80.

11 Celdrán A, Bazire P, García Ureña MA, Marijuán JL. H-hernioplasty: a tension-free repair for umbilical hernia. *Br J Surg* 1995, **82:** 371–2.

12 Britton BJ, Morris PJ. Local anesthesic hernia repair. An analysis of recurrence. *Surg Clin North Am* 1984; **64:** 245–55.

13 Yerdel MA, Akin EB, Dolalan S, Turkcapar AG, Pehlivan M, Gecim IE *et al.* Effect of single-dose prophylactic ampicillin and sulbactam on wound infection after tension-free inguinal hernia repair with polypropylene mesh: the randomized, double-blind, prospective trial. *Ann Surg* 2001; **233:** 26–33.

14 Nilsson F, Anderberg B, Bragmark M. Hernia surgery in a defined population. Improvements possible in outcome and cost effectiveness. *Am Surg* 1993; **1:** 150–3.

Association of Surgeons of Great Britain and Ireland

The annual meeting of the Association of Surgeons of Great Britain and Ireland was held in Birmingham, UK on 25–27 April 2001 under the Presidency of Mr D. F. L. Watkin. The abstracts of the presentations of the original work presented at the meeting have been published in a *BJS* supplement that accompanied the May 2001 issue of the Journal. The following articles are based on presentations from the Birmingham meeting and have been accepted for publication after peer review by the Journal's referees. Other papers from the meeting will appear in subsequent issues.

Extent of ductal carcinoma *in situ* within and surrounding invasive primary breast carcinoma

N. Crombie, R. S. Rampaul*, S. E. Pinder, C. W. Elston, J. F. R. Robertson* and I. O. Ellis

Departments of Histopathology and *Surgery, City Hospital NHS Trust, Nottingham, UK
Correspondence to: Dr I. O. Ellis, Department of Histopathology, City Hospital NHS Trust, Hucknall Road, Nottingham NG1 5NL, UK
(e-mail: ian.ellis@nottingham.ac.uk)

Background: The aim of this study was to evaluate the pathological and morphological features of ductal carcinoma *in situ* (DCIS) within and surrounding invasive ductal carcinoma, and to investigate its relationship with clinical outcome and established prognostic variables.
Methods: One hundred and seven patients with primary operable invasive breast carcinoma and associated DCIS treated by simple or subcutaneous mastectomy or wide local excision with radiotherapy were assessed. Those with pure DCIS and insufficient tumour available for examination were excluded. The most representative haematoxylin and eosin-stained sections from the remaining 91 samples were selected and examined at × 100 magnification using a 45-point, 2-mm grid graticule. The entire section was assessed and the cell under each point of the graticule was classed as either normal (a), DCIS surrounded by normal tissue (b), invasive tumour (c) or DCIS surrounded by invasive malignancy (d). The volume ratio of DCIS in the normal ($b/(a + b)$) and invasive ($d/(c + d)$) tissue was then calculated.
Results: The DCIS volume within invasive tumour was not associated with outcome. The DCIS volume within adjacent normal tissue, however, was associated with local recurrence ($P = 0{\cdot}025$), disease-free interval ($P = 0{\cdot}048$), the occurrence of distant metastases ($P = 0{\cdot}019$), death ($P = 0{\cdot}049$) and disease-free survival ($P = 0{\cdot}048$). Volume ratios of DCIS in normal and invasive tissue were not related to known prognostic factors including lymph node stage, grade, tumour size, vascular invasion or patient age.
Conclusion: There is a significant prognostic effect relating to the extent of DCIS associated with an invasive cancer, particularly with respect to local recurrence of tumour. This effect is restricted to the volume of DCIS in the tissue surrounding the invasive lesion rather than the intratumoral component.

Paper accepted 26 July 2001

British Journal of Surgery 2001, **88**, 1324–1329

Introduction

Ductal carcinoma *in situ* (DCIS) of the breast may be the principal precursor lesion for invasive breast cancer. In its pure form it accounts for about 5 per cent of patients presenting with a palpable breast lump and over 20 per cent in those undergoing mammographic screening. This increased detection rate has led to increasing interest in the biological behaviour and most appropriate treatment of the disease. Much of our understanding of the behaviour of

DCIS is based, however, on small series of lesions that had been biopsied but not surgically excised. The natural history and the optimal treatment of DCIS remain unclear[1–3], and several clinical trials are investigating the behaviour and therapy of 'pure' DCIS.

DCIS is commonly seen in association with invasive carcinomas but the proportion of DCIS varies markedly. The prognostic significance of DCIS seen in association with invasive breast carcinoma is not clear. The term 'extensive intraductal component' (EIC) has been used to define infiltrating ductal carcinoma in which intraductal carcinoma is prominent, occupying 25 per cent or more of the area encompassed by the infiltrating tumour, and intraductal carcinoma is present in sections of grossly normal adjacent breast tissue. Although EIC has been reported to be associated with an increased incidence of local recurrence of carcinoma, this has not been accepted universally and some groups have found no such correlation[3]. However, a consensus meeting of the European Organisation for Research on Treatment of Cancer concluded that 'the principal risk factor for local relapse after breast conserving treatment is large residual burden, and the main source of this burden is an extensive *in-situ* component which is found adjacent to 10–15 per cent of all invasive breast carcinoma'[4].

This study examined the relationship between the extent of DCIS surrounding, and within the boundaries of, an invasive primary breast cancer and sought any associations with other features in a series of well characterized invasive breast carcinomas.

Patients and methods

Patients

The 107 patients in this series presented consecutively with primary operable breast cancer to a single surgical team. A small number of patients with pure DCIS and those in whom insufficient tumour tissue was available for assessment were excluded, leaving a total of 91 tumours for study.

Patients were treated in a standard fashion by simple or subcutaneous mastectomy or wide local excision and radiotherapy. No systemic adjuvant therapy was given. At the time of surgery, lymph nodes were sampled. Tumours were measured in the fresh state in three perpendicular planes immediately after excision. Fresh tumour blocks were snap-frozen or fixed in neutral buffered formalin and embedded in paraffin wax for further assay. Histological grade[5], tumour type[6], vascular invasion[7] and oestrogen receptor status[8] were recorded for each tumour sample. The latter was assessed in these patients by a dextran-coated charcoal method and a cut-off of 10 fmol per mg protein was used for analysis.

Patients were followed after surgery at 3-month intervals for 18 months, every 6 months for 5 years, then annually. The disease-free interval was taken as the time in months from the date of the primary treatment to the first local, regional or distant recurrence. The overall survival was taken as the time in months from the date of the primary treatment to the time of death.

Morphometry

A block was chosen for each patient as the most representative section to include invasive tumour and normal tissue. A 3-μm section was cut and stained with haematoxylin and eosin. These sections were then examined at × 100 magnification using a 45-point, 2-mm grid graticule. The whole of each section was examined and the cell under each point of the graticule was classed as either normal, DCIS surrounded by normal tissue, invasive carcinoma or DCIS surrounded by invasive carcinoma. Areas that were without cells, for example owing to cystic or vascular spaces, were not included in the count.

For the purposes of analysis, the volume ratio of 'surrounding DCIS' was then calculated on the counts for DCIS occurring within otherwise normal tissue divided by the total count outside the invasive tumour (normal + DCIS) for each section. Similarly the volume ratio of DCIS within invasive tumour was calculated. These ratios were then used in statistical analyses, as the absolute quantity of cells in each category was not relevant.

Statistical analysis

Relationships between variables were sought using χ^2 analysis. All statistical analyses were performed using StatView® (4.1) software (Abacus Concepts, Berkeley, California, USA) on an Apple Macintosh computer (Apple, Cupertino, California, USA).

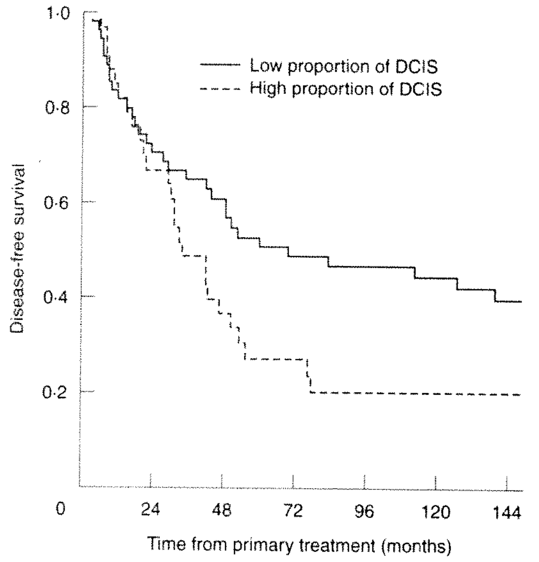
Results

The number of points counted per section in the 91 tumours ranged from 127 to 1517. The volume ratio of DCIS in normal tissue ranged from 0 to 0·54 (mean 0·17) and the volume ratio of DCIS in invasive tissue ranged from 0 to 0·31 (mean 0·10). The histograms of DCIS within normal tissue and DCIS within invasive cancer showed two potential groups based on the distribution at cut-offs of 0·2 and 0·09 respectively. These groups were then used for further analyses.

Table 1 Association of the ductal carcinoma *in situ* volume ratio with known prognostic factors, survival and recurrence in all patients with primary operable breast carcinoma

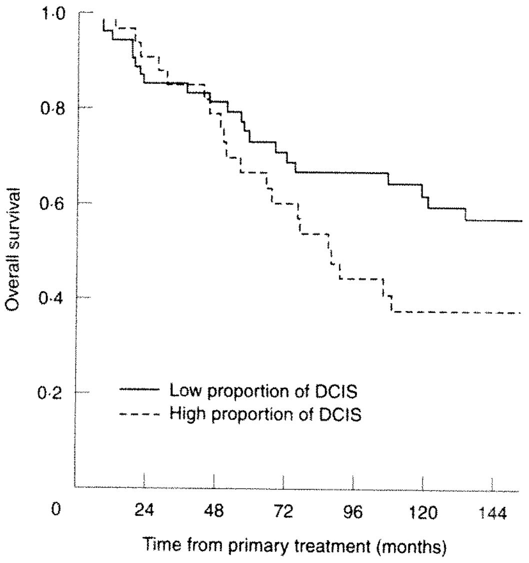
		DCIS in normal tissue		DCIS in invasive tissue	
Variable	Cut-offs	χ^2	*P*	χ^2	*P*
Age (years)	20–40, 41–50, 51–60, ≥ 61	2·67	0·446	4·51	0·212
Menopausal status	Pre- or post-menopausal	0·02	0·895	0·98	0·323
Tumour size (cm)	< 2·2, ≥ 2·2	2·87	0·090	0·68	0·410
Tumour grade	1, 2, 3	0·08	0·963	1·68	0·431
Stage	1, 2, 3	0·10	0·954	5·20	0·074
Oestrogen receptor status	10 fmol per mg protein	1·92	0·166	0·13	0·910
Distant metastases	Yes or no	5·53	0·019	0·00	0·987
Vascular invasion	None, probable, definite	0·58	0·748	1·20	0·550
Local recurrence	Yes or no	5·05	0·025	0·05	0·824
Regional recurrence	Yes or no	3·14	0·076	0·22	0·638
Disease-free interval		3·86	0·048	0·45	0·502
Overall survival		2·88	0·089	0·58	0·447
Death		3·88	0·049	0·29	0·589

DCIS, ductal carcinoma *in situ*



No. at risk							
Low proportion	54	38	30	24	21	19	16
High proportion	33	22	12	8	6	4	3

Fig. 1 Disease-free interval for patients with tumours showing low and high proportions of ductal carcinoma *in situ* (DCIS) (χ^2 = 3·86, *P* = 0·048)



No. at risk							
Low proportion	54	45	41	32	29	25	18
High proportion	33	30	25	19	14	7	4

Fig. 2 Overall survival for patients with tumours showing low and high proportions of ductal carcinoma *in situ* (DCIS) (χ^2 = 2·88, *P* = 0·089)

No association was seen between cytonuclear grade of DCIS and DCIS within the tumour (*P* = 0·379) or DCIS in the surrounding normal tissue (*P* = 0·204). The DCIS ratio in normal tissue showed different prognostic associations to the ratio of DCIS in invasive tissue. The latter was not linked statistically to any of the variables listed in *Table 1*. However, the ratio of DCIS in normal tissue was associated with local recurrence (*P* = 0·025), disease-free interval (*P* = 0·048) (*Fig. 1*), death (*P* = 0·049) and the occurrence of distant metastasis (*P* = 0·019). No statistical association with overall survival was seen (*P* = 0·089) (*Fig. 2*).

The results were then analysed according to the type of operation for the primary invasive breast cancer, i.e. wide local excision, subcutaneous mastectomy or simple mas-

Table 2 Association of ductal carcinoma *in situ* volume ratio with other prognostic factors, survival and recurrence in patients with primary operable breast carcinoma by operation

	Wide local excision (n = 15)				Subcutaneous mastectomy (n = 11)				Simple mastectomy (n = 65)			
	DCIS in normal tissue		DCIS in invasive tissue		DCIS in normal tissue		DCIS in invasive tissue		DCIS in normal tissue		DCIS in invasive tissue	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Local recurrence	5·83	0·015	0·89	0·346	6·52	0·011	0·63	0·429	0·41	0·524	1·14	0·286
Regional recurrence	5·83	0·016	0·89	0·349	6·52	0·011	0·62	0·429	0·06	0·807	2·17	0·141
Distant metastasis	3·75	0·053	1·78	0·673	3·75	0·530	1·29	0·257	0·86	0·355	2·68	0·101
Death	6·23	0·013	0·11	0·735	4·27	0·039	1·07	0·301	0·26	0·609	1·88	0·170
Overall survival	4·77	0·029	0·44	0·505	2·93	0·087	1·67	0·197	0·00	0·949	0·59	0·108

DCIS, ductal carcinoma *in situ*

tectomy (*Table 2*). The ratio of DCIS in the invasive tissue showed no significant association with recurrence of disease, distant metastasis or survival in the group of patients who had undergone simple mastectomy. In women who had selected wide local excision, however, a significant relationship between volume of DCIS in normal tissue and local recurrence (P = 0·015), regional recurrence (P = 0·016), death (P = 0·013) and survival (P = 0·029) was identified. Similarly, in patients who underwent subcutaneous mastectomy as treatment of choice, a significant association with local recurrence (P = 0·011), regional recurrence (P = 0·011) and death (P = 0·039) was seen.

Discussion

Recent studies have suggested that there is a relationship between the presence of EIC and local recurrence following surgical treatment for invasive breast cancer[9–13]. Other studies have found no such association[14–16]. These trials were performed in the USA where the trend has been for highly conservative surgery, removing minimal surrounding tissue (i.e. narrow margins). Pathology review in these series has largely concentrated on the intratumoral component, rather than the extratumoral component. It is important to appreciate that the influence of factors such as DCIS at the excision margin and the attendant risk of local recurrence is still unclear.

In this series the tumours were excised with a somewhat wider margin, allowing more extensive examination of both the intratumoral and extratumoral DCIS components. The DCIS was assessed in an objective and comprehensive fashion by morphometric assessment of the intratumoral and extratumoral components. In the early series of patients selected for this study there was (as in other studies) less emphasis on margin evaluation and indeed no clearly defined protocol as to what constituted complete excision. No associations were found with intratumoral DCIS and patient outcome variables but the volume of DCIS in the tissues surrounding the invasive component showed significant associations with local and regional recurrence as well as the development of distant metastatic disease, and disease-free and overall survival. In particular, the extent of DCIS surrounding the invasive carcinoma was associated with recurrence and survival in patients who chose wide local excision rather than simple mastectomy.

Recently, Park *et al.*[17] found that the local recurrence rate in patients with positive margins was significantly higher than that in patients with negative margins (27 *versus* 7 per cent). The authors concluded that pathological margin status was an important factor associated with local recurrence in breast-conserving surgery. The data from the present study also indicate that the extent of extratumoral DCIS is a predictor of local recurrence in primary operable breast carcinoma, particularly following breast-conserving surgery. This highlights the difficulty of assessing completeness of excision of DCIS either in a 'pure' form or in association with invasive carcinoma. Although the tumours in this series were believed to be completely excised, the higher rates of recurrence in patients with a greater volume of DCIS in the surrounding normal tissue suggest that residual DCIS was present and that the 'recurrence' might be classified more correctly as progression of residual disease. Indeed some studies have shown that the presence of an EIC predicts residual disease in re-excision specimens and it is not surprising that the residual disease is frequently DCIS[18–20]. Based on the present data it would seem that it is not EIC *per se* which indicates an increased risk of local recurrence but the presence of extensive DCIS outside the main invasive focus. This is almost certainly a better reflection of residual disease than EIC.

It has been suggested that limited breast resection may be acceptable for an EIC-negative tumour but that a more extensive resection is required for a tumour with an EIC[9]. Conversely, Schnitt *et al.*[21] demonstrated that none of the 30 patients with an EIC-positive tumour developed recurrence at the site of previous excision within 5 years if the margins were negative or close, but that 50 per cent did so when margins were more than focally positive. These same authors[22] reported that in patients with focally positive margins treated with conserving therapy and radiotherapy to the tumour bed there was a considerably lower risk of local recurrence than in those with more than focally positive margins.

The extent of DCIS outside the invasive tumour was also related to distant metastatic disease and survival. It is difficult to determine how DCIS extent might affect the development of metastatic disease, other than through the prognostic impact of the development of local recurrence. Previously local recurrence was not believed to have any long-term implications for patient survival, but recent data have indicated that patients who develop local recurrence have a poorer outcome than those who do not[23]. Patients with extensive DCIS around an invasive tumour may be more likely to have involved margins and to develop local recurrence and subsequent metastatic disease.

These findings contrast with those of the National Surgical Adjuvant Breast Project[3] and Anscher *et al.*[16]. Hurd *et al.*[15] also found that EIC did not adversely affect either survival or local control of breast cancer if complete excision (a 'negative margin') was obtained. Joura *et al.*[24] reported no association between EIC and either node status or survival and, while this study found no associations with locoregional recurrence in the whole population group, a relationship between locoregional recurrence and a higher volume of DCIS in the surrounding breast tissue was noted in patients treated with conservative surgery.

In conclusion, there is a significant prognostic effect of the extent of DCIS in association with invasive cancer, especially with respect to local recurrence. This, however, was related to the volume of DCIS in the tissue surrounding the tumour rather than the intratumoral component in women undergoing less than simple mastectomy. This almost certainly indicates an increased risk of 'occult' residual disease in the breast, with an associated increased risk of recurrence and consequently a poorer survival.

References

1 Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer* 1982; **49:** 751–8.

2 Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15–25 years after a diagnosis of low grade ductal carcinoma *in situ* of the breast treated only by biopsy. *Cancer* 1995; **76:** 1197–200.

3 Fisher ER, Sass R, Fisher B, Wickerham L, Paik SM. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). I. Intraductal carcinoma (DCIS). *Cancer* 1986; **57:** 197–208.

4 van Dongen JA, Fentiman IS, Harris JR, Holland R, Peterse JL, Salvadori B *et al. In-situ* breast cancer: the EORTC consensus meeting. *Lancet* 1989; **ii:** 25–7.

5 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991; **19:** 403–10.

6 Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. *Histopathology* 1992; **20:** 479–89.

7 Pinder SE, Ellis IO, Galea M, O'Rouke S, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship with recurrence and survival in a large study with long-term follow-up. *Histopathology* 1994; **24:** 41–7.

8 Maynard PV, Blamey RW, Elston CW, Haybittle JL, Griffiths K. Estrogen receptor assay in primary breast cancer and early recurrence of the disease. *Cancer Res* 1978; **38:** 4292–5.

9 Vicini FA, Eberlein TJ, Connolly JL, Recht A, Abner A, Schnitt SJ *et al.* The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. *Ann Surg* 1991; **214:** 200–4; Discussion 204–5.

10 Veronesi U, Luini A, Galimberti V, Zurrida S. Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute trials. *World J Surg* 1994; **18:** 70–5.

11 Jacquemier J, Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. An assessment of extensive intraductal component as a risk factor for local recurrence after breast-conserving therapy. *Br J Cancer* 1990; **61:** 873–6.

12 Borger J, Kemperman H, Hart A, Peterse H, van Dungen J, Bartelink H. Risk factors in breast-conservation therapy. *J Clin Oncol* 1994; **12:** 653–60.

13 Zafrani B, Vielh P, Fourquet A, Mosseri V, Durand JC, Salmon RJ *et al.* Conservative treatment of early breast cancer: prognostic value of the ductal *in situ* component and other pathological variables on local control and survival. *Eur J Cancer Clin Oncol* 1989; **25:** 1645–50.

14 Fisher B, Redmond C. Lumpectomy for breast cancer: an update of the NSABP experience. National Surgical Adjuvant Breast and Bowel Project. *J Natl Cancer Inst Monogr* 1992; **11:** 7–13.

15 Hurd TC, Sneige N, Allen PK, Strom EA, McNeese MD, Babiera GV *et al.* Impact of extensive intraductal component on recurrence and survival in patients with stage I or II breast cancer treated with breast conservation therapy. *Ann Surg Oncol* 1997; **4:** 119–24.

16 Anscher MS, Jones P, Prosnitz LR, Blackstock W, Hebert M, Reddick R *et al.* Local failure and margin status in early-stage breast carcinoma treated with conservation surgery and radiation therapy. *Ann Surg* 1993; **218**: 22–8.

17 Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, Gelman R *et al.* Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol* 2000; **18**: 1668–75.

18 Beron PJ, Horwitz EM, Martinez AA, Wimbish KJ, Levine AJ, Gustafson G *et al.* Pathologic and mammographic findings predicting the adequacy of tumour excision before breast-conserving therapy. *AJR Am J Roentgenol* 1996; **167**: 1409–14.

19 Campbell ID, Theaker JM, Royle GT, Coddington R, Carpenter R, Herbert A *et al.* Impact of an extensive *in situ* component on the presence of residual disease in screen detected breast cancer. *J R Soc Med* 1991; **84**: 652–6.

20 Wazer DE, Schmidt-Ullrich RK, Schmid CH, Ruthazer R, Kramer B, Safaii H *et al.* The value of breast lumpectomy margin assessment as a predictor of residual tumor burden. *Int J Radiat Oncol Biol Phys* 1997; **38**: 291–9.

21 Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB *et al.* The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer* 1994; **74**: 1746–51.

22 Gage I, Schnitt SJ, Nixon AJ, Silver B, Recht A, Troyan SL *et al.* Pathological margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 1996; **78**: 1921–8.

23 Shukla HS, Melhuish J, Mansel RE, Hughes LE. Does local therapy affect survival rates in breast cancer? *Ann Surg Oncol* 1999; **6**: 455–60.

24 Joura EA, Losch A, Kainz C, Sam C, Joura EM, Gitsch G *et al.* Infiltrating ductal carcinoma of the breast: extensive intraductal component has no impact on lymph node involvement and survival. *Anticancer Res* 1995; **15**: 2285–6.

Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients

G. Libertiny, C. J. E. Watson, D. W. R. Gray, K. I. Welsh and P. J. Morris

Oxford Transplant Centre, Churchill Hospital, Headington, Oxford, UK
Correspondence to: Mr G. Libertiny, Nuffield Department of Surgery, Level 6, John Radcliffe Hospital, Oxford OX3 9DU, UK
(e-mail: gabor.libertiny@surgery.oxford.ac.uk)

Background: The purpose of this study was to determine whether the incidence of post-transplant lymphoproliferative disease (PTLD) has been increasing in renal transplant recipients in this centre.

Methods: Prospectively gathered data were analysed to establish trends in the epidemiology of PTLD in 1537 patients.

Results: Overall, PTLD occurred in 2·3 per cent of renal transplant recipients. An increase in its incidence coincided with the introduction of cyclosporin in the 1980s. However, there was a further increase in the incidence of PTLD in the 1990s when the only change in immunosuppressive policy was the abandonment of pretransplantation blood transfusion. The latter increase was particularly pronounced in patients with early-onset PTLD in whom it presented within 600 days after transplantation.

Conclusion: The incidence of PTLD has been increasing in renal transplant recipients. The recent increase appears to be independent of cyclosporin and may reflect the reduction in pretransplant blood transfusion. Changes in the incidence of PTLD may also mirror changes in the epidemiology of non-Hodgkin lymphoma in the general population.

Paper accepted 23 July 2001

British Journal of Surgery 2001, **88**, 1330–1334

Introduction

The risk of developing malignancy in immunosuppressed organ transplant recipients is markedly increased compared with that in the general population[1]. After skin cancer, post-transplant lymphoproliferative disease (PTLD) is the most common such malignancy with a 28–49-fold increase in incidence compared with non-Hodgkin lymphoma in the general population[2]. PTLD carries a high mortality rate that approaches 70 per cent[3]. It occurs in 0–2·5 per cent of patients following renal transplantation[2]. The risk of developing PTLD differs according to the transplanted organ; the risk is lowest following renal transplantation and increases if the transplanted organ is heart, liver or heart–lung[4]. This difference may reflect the organ type, the level of immunosuppression used, and exposure to other recognized risk factors such as Epstein–Barr virus[3]. The type of immunosuppression also influences the risk of developing PTLD: cyclosporin-based regimens are associated with a higher risk than regimens containing only steroid and azathioprine[5,6]. Furthermore, PTLD develops sooner after transplantation in patients taking cyclosporin[6].

A recent increase in the number of patients presenting with PTLD prompted an examination of trends in its epidemiology in renal transplant recipients.

Patients and methods

Data of patients with PTLD diagnosed before June 1998 were obtained from the Oxford Transplant Centre Database, which includes a tumour registry and a large prospectively gathered database of all 1537 renal transplants performed between January 1975 and June 1998. PTLD was diagnosed by a consultant pathologist. The diagnosis of a lymphoid neoplasm was based on the morphology and, in most cases, immunophenotyping of tissue samples (*Table 1.*) The notes of patients found to have had lymphoma were studied in detail. Thirty-six patients, who arrived from overseas for living donor transplantation and were lost to follow-up after returning to their country, were excluded from the study. The follow-up on the remaining 1501 patients was 100 per cent complete, including all deaths and failed grafts. As the incidence of PTLD did not differ between men and women, or in recipients of first and subsequent transplants, these data were analysed together. The annual incidence of PTLD was compared for three time periods: 1976–1984, 1984–1989 and 1990 onwards. These intervals were based on the period when cyclosporin was introduced into clinical practice and on trends observed in the number of patients presenting with PTLD each year (*Fig. 1*). The database allowed examination of a wide range of factors including donor and recipient demographic data, original diagnosis, and aspects of dialysis, waiting time, donor and recipient human leucocyte antigen (HLA) matching, number of blood transfusions, operative details, details of immunosuppression, the number and treatment of rejection episodes, and follow-up data on renal function.

Statistical analysis

The χ^2 test and Fisher's exact test were used where appropriate. The annual incidence was calculated by determining the number of patients presenting with PTLD in a given year divided by the number of patients at risk, i.e. the cohort of patients with a working renal transplant and receiving immunosuppression. Although it is possible that a patient could present with PTLD after graft failure and the cessation of immunosuppressive drugs, this has not been observed. The annual incidences for the three time periods were compared with the Mann–Whitney *U* test. The renal transplant database was interrogated for simple relationships with KnowledgeSEEKER Software (ANGOSS Software Corporation, Toronto, Canada), which performs a large number of χ^2 tests. Selected variables were then analysed with a logistic regression technique. $P \leq 0{\cdot}05$ was considered significant.

Table 1 Site of post-transplant lymphoproliferative disease

Site	No. of patients
Gastrointestinal tract	10
Lung	4
Central nervous system	4
Adrenals	1
Transplant kidney	1
Diffuse	1
Skin	4
Lymph nodes	10

Results

PTLD was diagnosed in 35 of 1537 renal transplant recipients, giving an overall incidence of 2·3 per cent. The number of patients presenting with PTLD has increased in recent years (*Fig. 1*). While the number of patients with a working renal transplant grew steadily over the years, the rate at which patients presented with PTLD appeared to follow three different patterns. There were very few cases until 1983, followed by an increase to 0·8 per cent between 1984 and 1989, and a steeper increase to 2·3 per cent since 1990. The first increase coincided with the introduction of cyclosporin to this centre. Cyclosporin was introduced gradually from 1980 and became used routinely by 1984. By 1985 most patients received triple therapy, including cyclosporin, azathioprine and prednisolone. The initial cyclosporin dose was 10 mg per kg per day in 1985, changing later to 8 mg per kg per day. Doses of azathioprine (1·5 mg per kg per day) and prednisolone (20 mg per day) did not change during this period. Initial target trough levels of cyclosporin decreased from 400–800 to 150–300 ng/ml but this partly reflects the fact that different assays were used. Antilymphocyte globulin (ALG) was not

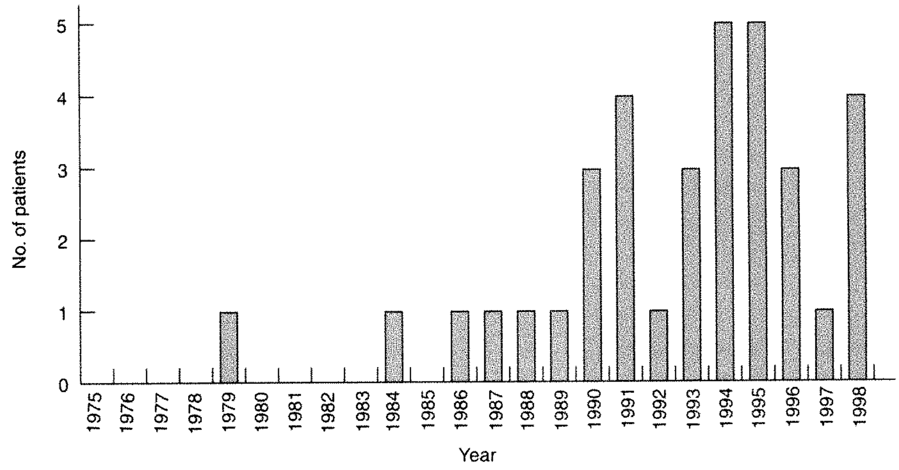


Fig. 1 Number of patients who presented each year with post-transplant lymphoproliferative disease

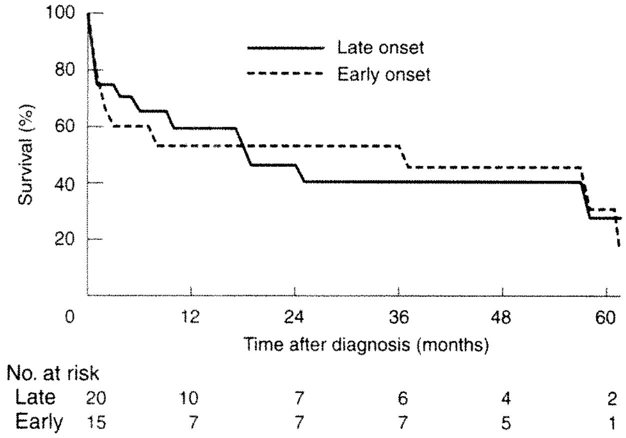


Fig. 2 Cumulative survival of patients with early- and late-onset post-transplant lymphoproliferative disease from the date of diagnosis

Table 2 Factors selected from the renal transplant database that showed a significant relationship with with the presence of early- and late-onset post-transplant lymphoproliferative disease in χ^2 tests

	P		
	All patients	Early onset	Late onset
Recipient age over 55 years	0·001	0·02	0·01
Unknown aetiology of renal failure	0·002†	0·009†	0·04
Cyclosporin	0·04	n.s.	n.s.
No. of blood transfusions < 5 units	n.s.	0·009	n.s.
Cold ischaemia time > 20 h	n.s.	0·01	n.s.
One or two *versus* no HLA-A matches	n.s.	0·008†	n.s.
Two *versus* no or one HLA-DR matches	n.s.	n.s.	0·002
Serum creatinine level*	0·001†	0·001	0·002†

*135–160 µmol/l inclusive at 2 years *versus* other values. HLA, human leucocyte antigen; n.s., not significant. †Variables in each subgroup that remained significant with logistic regression

given routinely. However, when ALG was administered it was recorded in the transplant database together with the type of antibody used. The annual incidence of PTLD in 1984–1989 was significantly higher than that in the preceding period (P = 0·03, Mann–Whitney U test). The increase between 1990 and 1998 was also significant compared with the level observed in 1984–1989 (P = 0·03). At this time no change in immunosuppressive policy took place other than the abandonment of pretransplantation blood transfusion.

PTLD presented as early as 4 months following transplantation and occurred as late as 19 years after the start of immunosuppression. There appeared to be an interval from 520 to 800 days after operation when no PTLD was diagnosed. Therefore patients with PTLD were divided into an early-onset subgroup (within 600 days of transplantation; 15 patients) and a late-onset subgroup (more than 600 days; 20 patients). The annual incidence of early-onset PTLD in patients at risk of this (i.e. those with a working kidney that was transplanted less than 600 days before a given date) was on average four times higher in 1990–1998 than in 1984–1989 (P = 0·013, Mann–Whitney U test). Obviously, the incidence of late-onset PTLD in recently transplanted patients is not known. There was no significant difference between the early- and late-onset subgroups with respect to age (P = 0·80, Mann–Whitney U test) and whether cyclosporin was given (χ^2 = 0·09, 1 d.f., P = 0·75). Survival was equally poor in both early and late subgroups; approximately 40 per cent of patients were still alive 5 years after the diagnosis of PTLD (*Fig. 2*).

Table 2 shows variables related to the development of PTLD or its subgroups that were selected with χ^2 tests from the renal transplant database. Administration of any form of ALG, including OKT3, did not appear to influence the incidence of PTLD, nor did cumulative steroid dose, absence or presence of rejection, or other immunosuppressive agents such as tacrolimus or mycophenolate mofetil. All but one patient with PTLD had a cadaveric transplant. However, the incidence of PTLD in patients with a cadaveric transplant was not significantly higher than that in recipients of a living related transplant (P = 0·15, Fisher's exact test). The increase in incidence of PTLD at the beginning of the 1990s coincided with abandoning the policy of deliberate pretransplantation blood transfusion. The association between the amount of blood transfused and the development of PTLD was apparent only in the case of early-onset disease (*Table 2*). However, only the total amount of preoperative blood transfused was recorded in the database, which included units of blood given for anaemia long before the transplantation.

A logistic regression test was carried out with the variables shown in *Table 2*. PTLD was more likely to develop in recipients in whom the cause of the original renal failure was uncertain (P = 0·05) and whose serum creatinine level was between 135 and 160 µmol/l 2 years after the operation (P = 0·016). The development of early-onset PTLD was found to be more common in patients with one or two *versus* no HLA-A matches (P = 0·007) and in whom the cause of the renal failure was unknown (P = 0·02). In ten of 15 patients with early-onset PTLD the transplanted kidney failed in less than 2 years following the transplantation. Therefore in this group of patients the biannual serum creatinine value was not included in the logistic regression model. The late-onset group only showed a relationship between PTLD and the serum creatinine level 2 years after transplantation on logistic regression analysis ($P = 0.02$).

Discussion

PTLD developed in 2·3 per cent of patients transplanted in this centre. This rate is higher than is usually reported[2]. Importantly, the rate at which patients with PTLD present has been increasing. An initial increase coincided with the introduction of cyclosporin into regular clinical practice by 1984. However, there was a second increase in the annual incidence of PTLD from 1990 onwards. As it was most pronounced in patients with early-onset PTLD (within 600 days of transplantation), this second rise cannot be attributed to a prolonged cyclosporin effect. One hypothesis may be based on the observation of a higher incidence of early-onset disease in patients who had fewer blood transfusions, despite the fact that the overall number of blood transfusions did not remain significant when logistic regression analysis was used (*Table 1*). However, abandonment of deliberate pretransplant blood transfusion appears to have been the only identifiable change in immunosuppression policy at the time of the second rise in the annual incidence of PTLD. According to this hypothesis patients with fewer blood transfusions may not have encountered Epstein–Barr virus before transplantation and may have contracted it from the kidney at the time of transplantation while they were immunosuppressed. If the patients acquired the virus with the kidney it is unclear why there was a delay in disease onset. The administration of acyclovir for treatment of cytomegalovirus infection may have influenced disease onset. The hypothesis also assumes that the blood-transfused patients contracted the virus from blood donors while immunocompetent. Alternatively, blood transfusion may lower the overall dosage of immunosuppression required to maintain the graft or have another beneficial immunological effect. A prospective randomized trial of blood transfusion has been shown recently to produce a marked graft survival benefit in patients taking cyclosporin[7], which is consistent with this concept.

It is generally accepted that the incidence of PTLD has increased with the introduction of cyclosporin-containing immunosuppressive regimens[2,5,6]. In multicentre studies[5,6] cyclosporin will have an increased weight in statistical analysis as it is one of the most important common denominators among transplant centres all over the world, but other and possibly local factors influencing the development of PTLD lose their statistical significance. This is illustrated in other reports from single centres where the weight of cyclosporin is reduced[8,9].

It will require further investigation to explain the relationship between PTLD and associated factors obtained from the renal transplant database. It is possible that some or all of the associations found are spurious and represent a type I statistical error. The finding of an association between PTLD and a serum creatinine level between 135 and 160 μmol/l on follow-up may be attributed to patients with certain immunological characteristics that render them more susceptible to PTLD.

An uncertain cause of the original chronic renal failure was also significantly associated with PTLD. This may be due to an as yet unknown pathology in the kidney or reflect a longer period of deteriorating renal function preceding the diagnosis, as chronic renal failure increases the likelihood of developing malignancy in its own right[10]. The role of HLA-A matching in patients with early-onset PTLD, and HLA-DR match on simple comparison in the late-onset form, highlights the differences between these subgroups. Some variables that were significant on simple comparison, such as age and cold ischaemia time, may also be important (*Table 2*). However, it must be remembered that multiple analyses will find some spurious associations by chance. Because there has been no apparent alteration in these factors other than transfusion, it seems unlikely that they explain fully why PTLD occurs with increasing frequency. Interestingly, the incidence of non-Hodgkin lymphoma in the general population has also been increasing[11]. Several, mostly unrecognized, environmental factors are thought to be responsible for this. PTLD is much more common in renal transplant recipients than non-Hodgkin lymphoma in the general population and an increase in its incidence is consequently more noticeable. It is feasible that transplant recipients with PTLD in effect provide a model for what appears to be occurring with non-Hodgkin lymphoma in the general population. This hypothesis will be supported if the present findings are confirmed by other transplant centres.

References

1 Morrison VA, Dunn DL, Manivel JC, Gajl-Peczalska KJ, Peterson BA. Clinical characteristics of post-transplant lymphoproliferative disorders. *Am J Med* 1994, **97**: 14–24.

2 Boubenider S, Hiesse C, Goupy C, Kriaa F, Marchand S, Charpentier B. Incidence and consequences of post-transplantation lymphoproliferative disorders. *J Nephrol* 1997; **10**: 136–45

3 Thomas JA, Crawford DH, Burke M. Clinicopathologic implications of Epstein–Barr virus related B cell lymphoma in immunocompromised patients. *J Clin Pathol* 1995; **48**: 287–90.

4 Nalesnik MA, Jaffe R, Starzl TE, Demetris AJ, Porter K, Burnham JA *et al*. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporin A–prednisone immunosuppression. *Am J Pathol* 1988; **133**: 173–92.

5 Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993; **342:** 1514–16.

6 Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991; **23:** 1101–3.

7 Opelz G, Vanrenterghem Y, Kirste G, Gray DW, Horsburgh T, Lachance JG *et al.* Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. *Transplantation* 1997; **63:** 964–7.

8 Sheil AG, Disney AP, Mathew TH, Livingston BE, Keogh AM. Lymphoma incidence, cyclosporine, and the evolution and major impact of malignancy following organ transplantation. *Transplant Proc* 1997; **29:** 825–7.

9 Hiesse C, Kriaa F, Rieu P, Larue JR, Benoit G, Bellamy J *et al.* Incidence and type of malignancies occurring after renal transplantation in conventionally and cyclosporine-treated recipients: analysis of a 20-year period in 1600 patients. *Transplant Proc* 1995; **27:** 972–4.

10 Fahlenkamp D, Reinke P, Kirchner S, Schnorr D, Lindeke A, Loening SA. Malignant tumours after renal transplantation. *Scand J Urol Nephrol* 1996; **30:** 357–62.

11 Vineis P. Incidence and time trends for lymphomas, leukemias and myelomas: hypothesis generation. Working Group on the Epidemiology of Hematolymphopoietic Malignancies in Italy. *Leuk Res* 1996; **20:** 285–90.

Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm

T. E. Rowlands and S. Homer-Vanniasinkam

Vascular Surgical Unit, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK
Correspondence to: Professor S. Homer-Vanniasinkam (e-mail. sherhv@ulth.northy.nhs.uk)

Background: Pro- and anti-inflammatory cytokine release occurs with abdominal aortic aneurysm (AAA) repair although the relative contribution of each is currently poorly understood. Ischaemia–reperfusion injury is thought to play a greater role following open (OR) than endovascular (ER) repair, with resultant greater perioperative morbidity.

Methods: Thirty-two patients undergoing OR ($n = 16$) and ER ($n = 16$) of AAA were studied. Systemic venous (SV) blood was taken at induction (baseline), 0 h (last clamp off), 4, 24, 72 and 144 h, and femoral venous (FV) blood (indwelling catheter; lower torso venous effluent) at 0, 4 and 24 h. The cytokines interleukin (IL) 6, IL-8 and IL-10 were measured in these samples.

Results: In OR, SV and FV IL-6 increased from baseline to a peak at 24 h (SV 589 pg/ml ($P = 0{\cdot}001$ *versus* baseline) and FV 848 pg/ml ($P = 0{\cdot}05$)) before declining at 144 h. In ER, there was a similar pattern but the increase was smaller (24 h: SV 260 pg/ml ($P = 0{\cdot}003$ *versus* baseline) and FV 319 pg/ml ($P = 0{\cdot}06$)) at all equivalent timepoints compared with OR. IL-8 peaked earlier (4 h) from baseline in both groups before declining by 144 h, and significant differences between SV and FV were seen only in the OR group. IL-10 levels peaked in both groups at 24 h before declining at 144 h, and there were no significant locosystemic differences between the groups.

Conclusion: Venous pro-inflammatory cytokine changes (IL-6) are consistent with significantly greater lower-torso reperfusion injury in patients undergoing OR. Smaller responses were seen after ER (IL-6 and IL-8), although both groups showed a similar anti-inflammatory response (IL-10); this pro- and anti-inflammatory imbalance may account for the increased morbidity assoicated with OR.

Paper accepted 24 July 2001

British Journal of Surgery 2001, 88, 1335–1340

Introduction

Conventional open surgery for abdominal aortic aneurysm (AAA) carries a considerable risk of morbidity and death[1]. The recognition that there were potential benefits in reducing the time of aortic cross-clamping, avoiding a large abdominal incision and decreasing the effects of intra-abdominal manipulation of the viscera led to the search for an alternative means of repairing AAA. The description of transfemoral endovascular stent placement may be perceived as the most significant development in this area[2]. The technique has gained wide acceptance, with a proliferation in the variety of graft devices and the centres carrying out the procedure.

Despite the promise of reductions in morbidity and mortality rates, concerns remain about the safety and long-term results of endovascular stenting[3,4]. Ischaemia–reperfusion injury (IRI)[5] is thought to play a greater role following open (OR) than endovascular (ER) repair, with resultant greater perioperative morbidity. ER theoretically avoids the effects of prolonged aortic cross-clamping, as occurs in OR, although the lower limbs may still be subjected to short periods of ischaemia. Pro- and anti-inflammatory cytokine release must therefore occur with all AAA repairs whether by the open or endovascular technique. The relative contribution of each aspect of this pro- and anti-inflammatory response is currently poorly understood. Differential expression of cytokines may occur and such imbalances may contribute to postoperative complications[6].

This study attempted to: (1) determine whether ER is associated with a smaller pro-inflammatory perioperative response; (2) determine whether there is a proportional anti-inflammatory response (the so-called T helper (Th) cell type 1/Th2 response); and (3) establish whether local venous sampling from the femoral vein gives a better indication of reperfusion-related events than conventional systemic sampling.

Patients and methods

All study procedures were approved by the local ethics committee. Thirty-two consecutive patients for AAA repair gave written consent for the study. The demographic details are shown in *Table 1*. Sixteen patients with infrarenal AAA who met the anatomical criteria underwent stent placement via the transfemoral route. The stents used were supplied by Endovascular Technologies® (Menlo Park, California, USA) and W. L. Gore® (Flagstaff, Arizona, USA). The main exclusion criteria for an ER were a short infrarenal neck and/or dilated, tortuous or occluded iliac arteries. The other 16 patients underwent OR. All patients were operated on under general anaesthesia.

Systemic venous (SV) blood samples were taken at induction (baseline) and at 0, 4, 24, 72 and 144 h after cross-clamp removal. A cannula (Vygon Leadercath® 16Ch; Vygon, Aachen, Germany) was placed into the femoral vein by the Seldinger technique before clamping the common femoral artery. This remained *in situ* for the first 24 h after operation, allowing femoral venous (FV) samples to be taken at 0, 4 and 24 h after clamp removal, to correspond with the respective peripheral samples. The time restraint of 24 h on the FV sampling was imposed by the ethics committee.

At each timepoint, approximately 20 ml of blood was drawn from the antecubital fossa and/or the femoral vein cannula as appropriate. The blood was immediately separated into 10-ml containers for serum and ethylenediamine tetra-acetic acid–plasma (Sarstedt, Numbrecht, Germany), and then centrifuged within 10 min at 4°C for 15 min at 2500*g* (Heraeus Sepatech, Hanau, Germany). The serum and plasma were then pipetted in 0·4-ml aliquots into 2-ml polypropylene microtubes (Sarstedt), and were immediately frozen and stored at −80°C.

Interleukin (IL) 6, IL-8 and IL-10 were analysed by well established enzyme-linked immunosorbent assays, using commercially available matched monoclonal and biotinylated antibody pairs (R and D Systems, Minneapolis, Minnesota, USA).

Cytokine levels are given as mean values in the text. Data were analysed by one-way analysis of variance. Where data were non-parametric the Wilcoxon and Mann–Whitney *U* tests were used for comparison within and between the study groups respectively.

Results

In the OR group there was one death from myocardial infarction on day 5 after operation. There were no perioperative deaths in the ER group. Four patients in the ER group developed minor wound infections in one or both groins, compared with five patients in the OR group who had abdominal wound infections. Two patients in the OR group developed postoperative renal impairment requiring temporary renal support; both recovered spontaneously. Fifteen of the 16 patients in the ER group developed pyrexia (fever greater than 38°C) on the second or third day after operation; this phenomenon was not seen in the OR group.

In the OR group preliminary analysis of the cytokines showed no differences between tube and bifurcated graft use, so these are considered together.

Interleukin 6

SV IL-6 concentration was significantly greater after OR than ER at all equivalent timepoints (*Fig. 1*). In the OR group IL-6 increased from baseline to a peak at 24 h (9 *versus* 589 pg/ml; P = 0·001) before declining at 144 h (112 pg/ml; P = 0·007). There was a similar pattern but a smaller increase in IL-6 level in the ER group (10 pg/ml at baseline *versus* 260 pg/ml at 24 h; P = 0·003). In the OR group FV IL-6 concentration was higher at all equivalent timepoints than the systemic level (0 h: 169 *versus* 130 pg/ml (P = 0·003); 4 h: 520 *versus* 389 pg/ml (P = 0·08); 24 h: 848 *versus* 589 pg/ml (P = 0·03)) (*Fig. 2*). FV IL-6 concentration increased to 24 h after cross-clamp removal in the OR group (9 *versus* 848 pg/ml; P = 0·05); this level was significantly higher than that in the ER group (848 *versus*

Table 1 Patient and treatment data for 32 patients treated by open or endovascular repair

	Open	Endovascular
Median (range) age (years)	74·5 (62–82)	76·0 (60–87)
Sex ratio (M : F)	11 : 5	14 : 2
Diameter of aneurysm (mm)	58	63
Graft type		
Tube	5	
Bifurcated	11	
Operating time (min)	169	189
Aortic cross-clamp time (min)	82·5	n.a.
Length of stay (days)	9	7
Intraoperative fluid requirement		
Blood (ml)	780	340
Colloid/crystalloid (ml)	5250	3300
Postoperative fluid requirement		
Blood (ml)	266	176

Values given as mean unless otherwise stated. n.a., Not applicable

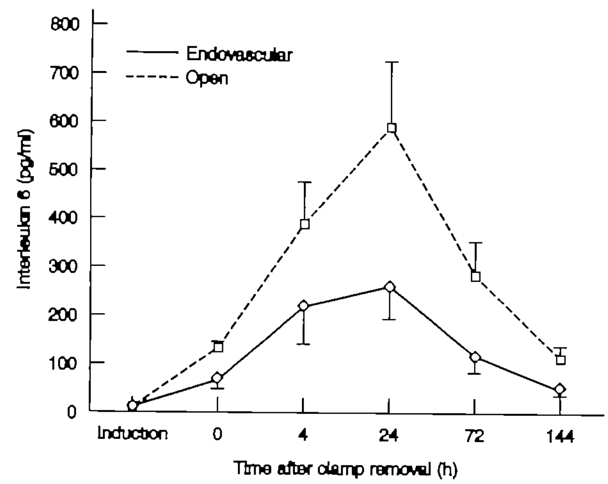


Fig. 1 Mean(s.e.m.) systemic interleukin 6 levels in open and endovascular repair groups

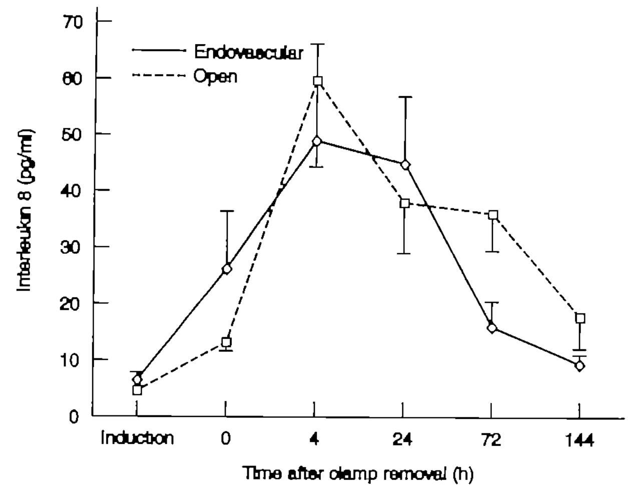


Fig. 3 Mean(s.e.m.) systemic interleukin 8 levels in open and endovascular repair groups

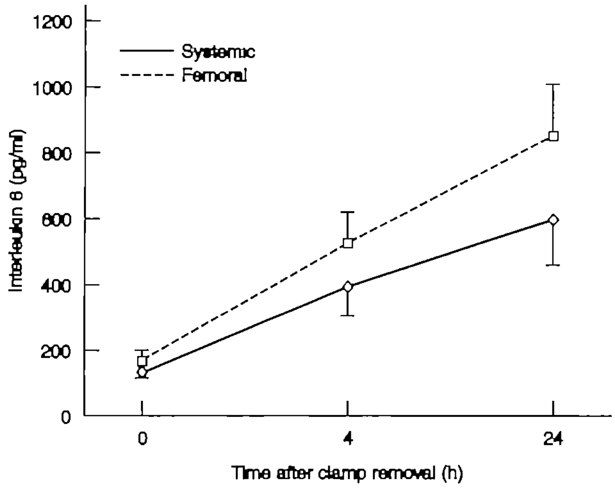


Fig. 2 Comparison of systemic and femoral interleukin 6 levels in open repair group. Values are mean(s.e.m.)

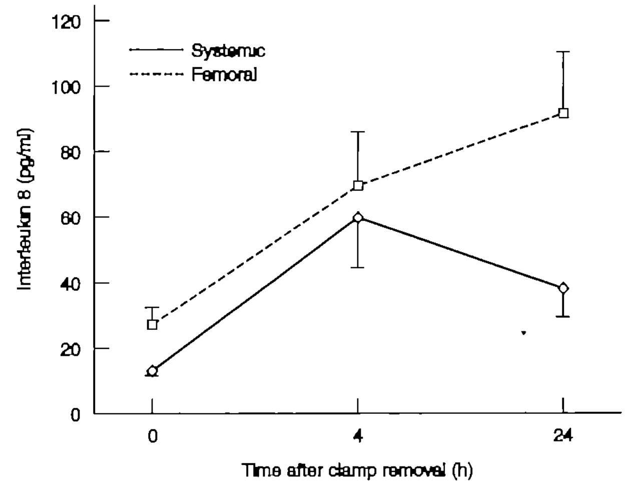


Fig. 4 Comparison of systemic and femoral interleukin 8 levels in open repair group. Values are mean(s.e.m.)

319 pg/ml; *P* = 0·007), which rose to 319 pg/ml from 10 pg/ml baseline (*P* = 0·06). The ER group appeared to show slight locosystemic differences in IL-6 level but these were not significant (SV *versus* FV at 0 h: 65 *versus* 64 pg/ml (*P* = 0·73); 4 h: 216 *versus* 223 pg/ml (*P* = 0·36); 24 h: 260 *versus* 319 pg/ml (*P* = 0·59)).

Interleukin 8

SV IL-8 concentration peaked earlier at 4 h from baseline in both OR (5 pg/ml at baseline *versus* 60 pg/ml at 4 h; *P* = 0·003) and ER (7 *versus* 49 pg/ml; *P* = 0·024) groups before declining by 144 h (*Fig. 3*). This decline appeared to occur more quickly in the ER group (at 72 h: OR 35 pg/ml and ER 16 pg/ml; *P* = 0·001 and *P* = 0·015 *versus* respective baselines). In the OR group FV IL-8 levels were significantly higher than SV levels at 0 and 24 h (0 h: 27 *versus* 13 pg/ml (*P* = 0·01); 24 h: 90 *versus* 38 pg/ml (*P* = 0·01)); these differences were not noted at 4 h (69 *versus* 59 pg/ml; *P* = 0·3) (*Fig. 4*). No significant locosystemic differences were noted in the ER group (FV *versus* SV at 0 h: 32 *versus* 26 pg/ml; 4 h: 59 *versus* 49 pg/ml; 24 h: 51 *versus* 45 pg/ml).

Interleukin 10

From baseline, SV IL-10 levels peaked in both groups at 24 h before declining at 144 h, and there were minimal differences between the OR and ER groups (baseline 6 *versus* 7 pg/ml ($P = 0{\cdot}7$); 0 h: 34 *versus* 37 pg/ml ($P = 0{\cdot}44$); 4 h: 66 *versus* 75 pg/ml ($P = 0{\cdot}52$); 24 h: 141 *versus* 118 pg/ml ($P = 0{\cdot}45$); 72 h: 98 *versus* 103 pg/ml ($P = 0{\cdot}11$); 144 h: 77 *versus* 55 pg/ml ($P = 0{\cdot}18$)). There were no significant locosystemic differences noted in the OR and ER groups.

Discussion

Operative trauma, as measured using conventional markers such as platelet count, C-reactive protein (CRP) and IL-6 in previous studies[7], has been shown to be reduced in ER compared with OR[8]. Length of stay in hospital is shorter, as are fluid and transfusion requirements.

Pyrexia after endovascular stent insertion for AAA has been described and may have several potential aetiologies including bacterial translocation due to transient splanchnic ischaemia[9] and IL-6 release. Pyrexia following endovascular stent insertion has been described as the 'post-implantation syndrome' by other investigators, the aetiology and significance of which remains unknown[10]. Endotoxaemia can itself induce IL-6 and tumour necrosis factor (TNF) α release[11,12] and there are high levels of IL-6 in cell supernatants from the thrombus removed from AAA in OR[13]. In this study, postoperative pyrexia was commonly seen in patients undergoing stent repair around day 3; the 24-h peak of IL-6 observed would therefore not be expected to correlate with this. Syk *et al.*[14] similarly found no correlation between IL-6 levels and the presence of pyrexia, although they incidentally noted no difference between postoperative pyrexia in patients undergoing OR or ER.

IL-6 is a well described cytokine secreted by a variety of cellular sources, including monocytes, endothelial cells, T lymphocytes, neutrophils and macrophages[15]. Among its many functions is induction of the hepatic acute-phase proteins, including CRP, and so it may be the predominant mediator of the postoperative acute-phase response[16]. IL-6 is pleiotropic in its functions, and so raised levels have been considered detrimental in other studies[17]. Rising levels of IL-6 in OR[18] and ER have been demonstrated previously[8,19,20]; possible causes include the presence of IRI, exposure of leucocytes to graft material, and operative trauma from the abdominal incision in OR. Lower levels of IL-6 have been noted with endovascular stent repair[10]. This group noted peak IL-6 levels in open AAA repair at 24 h, similar to the present study, but with an earlier 6-h peak in the endovascular group. This was a smaller study of 14 patients.

Other studies have shown the converse: higher levels of IL-6 in ER together with higher granulocyte elastase levels[21]. This may result from the mass effect of aneurysmal thrombus during stent deployment.

Locosystemic differences in IL-6 levels have been described previously; in a myocardial model of IRI involving recanalization of the left anterior descending artery, the IL-6 level was raised in coronary sinus blood relative to arterial blood[22]. In the present study IL-6 levels were higher in the FV effluent following aortic occlusion in open AAA repair, indicating that a degree of IRI had occurred.

IL-8 is a potent pro-inflammatory cytokine secreted from a variety of sources with multiple stimuli[23]. It is a potent chemoattractant and activator of neutrophils[24–27], pivotal to the development of IRI[28,29]. Patients undergoing major surgery, including AAA repair, have been shown to have high circulating IL-8 levels, which may be proportional to the magnitude of the stimulus. Froon *et al.*[30] demonstrated IL-8 release in AAA repair, which was far greater in the presence of shock, during acute AAA rupture. As such, raised levels of IL-8 have been correlated with poor prognosis in patients subsequently developing pulmonary dysfunction[31] and multiple organ failure[32]. Other small studies have shown no difference in IL-8 release between open and endovascular repair[21]. In this study open AAA repair was associated with greater locosystemic differences in IL-8 release than ER, demonstrating that measurable IRI had occurred following OR, which was not seen in the endovascular group. The raised femoral venous IL-8 level may be explained by greater endothelial–neutrophil interaction with inflammatory cell chemotaxis in the lower-limb vasculature[33], with subsequent clearance of the IL-8 from the systemic circulation[34].

IL-10 is pleiotropic, but has predominantly anti-inflammatory activity. It is involved in the regulation of macrophage and T-cell function, and inhibits IL-1α, IL-8 and TNF-α production *in vitro*[35]. It appears to be a potent modulator of neutrophil activity *in vitro*[36] and has been used experimentally as an administered compound specifically to reduce the sequelae of neutrophil activation[37]. IL-10 may be expressed concurrently with pro-inflammatory cytokines in response to major stimuli[38,39]. In the present study raised levels were detected in both the open and endovascular groups, and were maximal at 24 h after cross-clamp removal; there were no significant differences between the groups, implying that the magnitude of this anti-inflammatory response was similar for each group. In a study of open AAA repair, the IL-10 level was similarly noted to be maximal at 24 h after repair, with detectable residual activity at 1 week[40]. The presence of peak levels of IL-10 appears to vary, with other investigators demonstrating an earlier monophasic rise and decline[41]. The latter study showed similar levels to those in the present investigation, albeit at earlier timepoints (peak levels at 30 min after cross-clamp removal) but interestingly showed a fourfold increase in levels in thoracoabdominal aneurysm repair, correlating with the length of visceral ischaemia, in particular the gut. IL-10 has also been detected in the early stages of the repair itself[20], demonstrating that early immunological activity rather than a stimulus such as IRI may have provoked release. The present results support the hypothesis that IL-10 release is not IRI dependent under the conditions of the study as the presence of prolonged aortic cross-clamping in OR made no difference to IL-10 release. It cannot be concluded that IL-10 indirectly reflects an increased pro-inflammatory response. The source of the IL-10 did not seem to be the lower limb and torso as there was no measurable locosystemic difference, a finding similar to that reported elsewhere[41].

With open aortic surgery, the lower-limb musculature can undergo degradative ultrastructural changes which are initiated during the period of relative ischaemia with aortic cross-clamping, and which become worse with subsequent reperfusion[42]. By reducing the duration of prolonged cross-clamping of the aorta, ER may reduce IRI. Free radical production, IL-1β and TNF-α were reduced in a small study of six patients undergoing ER by this same group, thus demonstrating a reduction in neutrophil-related mediator release, typical of IRI[43].

Open AAA repair is associated with a greater pro-inflammatory response. IL-6 and IL-8 were present in greater quantities after OR than ER. These levels were reflected both locally from the FV effluent, and systemically. The higher FV levels of IL-6 may provide a more direct clinical marker of IRI, demonstrating greater inflammatory activity downstream of the aortic repair. In contrast, lower inflammatory activity in terms of IL-6 and, to a lesser extent, IL-8 release was seen in the endovascular group, indicating that the procedure as a whole causes less surgical trauma. The anti-inflammatory response was similar in both groups. This imbalance in the Th1 *versus* Th2 cytokine profile may explain the potential for greater morbidity in patients undergoing OR of AAA.

References

1 Berridge DC, Chamberlain J, Guy AJ, Lambert D. Prospective audit of abdominal aortic aneurysm surgery in the northern region from 1988 to 1992. Northern Vascular Surgeons Group. *Br J Surg* 1995; **82**: 906–10.

2 Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991; **5**: 491–9.

3 May J, White GH, Yu W, Ly CN, Waugh R, Stephen MS *et al.* Concurrent comparison of endoluminal *versus* open repair in the treatment of abdominal aortic aneurysms: analysis of 303 patients by life table method. *J Vasc Surg* 1998; **27**: 213–20.

4 White GH, May J, McGahan T, Yu W, Waugh RC, Stephen MS *et al.* Historic control comparison of outcome for matched groups of patients undergoing endoluminal *versus* open repair of abdominal aortic aneurysms. *J Vasc Surg* 1996; **23**: 201–11.

5 Grace PA. Ischaemia–reperfusion injury. *Br J Surg* 1994; **81**: 637–47.

6 Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. *Crit Care Med* 1996; **24**: 163–72.

7 Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; **340**: 448–54.

8 Odegard A, Lundbom J, Myhre HO, Hatlinghus S, Bergh K, Waage A *et al.* The inflammatory response following treatment of abdominal aortic aneurysms: a comparison between open surgery and endovascular repair. *Eur J Vasc Endovasc Surg* 2000; **19**: 536–44.

9 Zhi-Yong S, Dong YL, Wang XH. Bacterial translocation and multiple system organ failure in bowel ischemia and reperfusion. *J Trauma* 1992; **32**: 148–53.

10 Swartbol P, Norgren L, Albrechtsson U, Cwikiel W, Jahr J, Jonung T *et al.* Biological responses differ considerably between endovascular and conventional aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 1996; **12**: 18–25.

11 Dinarello CA, Cannon JG, Wolff SM, Bernheim HA, Beutler B, Cerami A *et al.* Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin 1. *J Exp Med* 1986; **163**: 1433–50.

12 Wortel CH, van Deventer SJ, Aarden LA, Lygidakis NJ, Buller HR, Hoek FJ *et al.* Interleukin-6 mediates host defence responses induced by abdominal surgery. *Surgery* 1993; **114**: 564–70.

13 Swartbol P, Truedsson L, Norgren L. Adverse reactions during endovascular treatment of aortic aneurysms may be triggered by interleukin 6 release from the thrombotic content. *J Vasc Surg* 1998; **28**: 664–8.

14 Syk I, Brunkwall J, Ivancev K, Lindblad B, Montgomery A, Wellander E *et al.* Postoperative fever, bowel ischaemia and cytokine response to abdominal aortic aneurysm repair – a comparison between endovascular and open surgery. *Eur J Vasc Endovasc Surg* 1998; **15**: 398–405.

15 Akira S, Hirano T, Taga T, Kishimoto T. Biology of multifunctional cytokines: IL 6 and related molecules (IL 1 and TNF). *FASEB J* 1990; **4**: 2860–7.

16 Heath DI, Cruickshank A, Gudgeon M, Jehanli A, Shenkin A, Imrie CW. Role of interleukin-6 in mediating the acute phase protein response and potential as an early means of severity assessment in acute pancreatitis. *Gut* 1993; **34**: 41–5.

17 Schluter B, Konig B, Bergmann U, Muller FE, Konig W. Interleukin-6 – a potential mediator of lethal sepsis after major thermal trauma: evidence for increased IL-6 production by

peripheral blood mononuclear cells. *J Trauma* 1991; **31:** 1663–70.

18 Groeneveld AB, Raijmakers PG, Rauwerda JA, Hack CE. The inflammatory response to vascular surgery-associated ischaemia and reperfusion in man: effect on postoperative pulmonary function. *Eur J Vasc Endovasc Surg* 1997; **14:** 351–9.

19 Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; **79:** 757–60.

20 Holzheimer RG, Gross J, Schein M. Pro- and anti-inflammatory cytokine-response in abdominal aortic aneurysm repair: a clinical model of ischemia–reperfusion. *Shock* 1999; **11:** 305–10.

21 Morikage N, Esato K, Zenpo N, Fujoka Y, Takenaka H. Is endovascular treatment of abdominal aortic aneurysms less invasive regarding the biological responses? *Surg Today* 2000; **30:** 142–6.

22 Neumann FJ, Ott I, Gawaz M, Richardt G, Holzapfel H, Jochum M *et al.* Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation* 1995; **92:** 748–55.

23 Matsushima K, Oppenheim JJ. Interleukin 8 and MCAF: novel inflammatory cytokines inducible by IL 1 and TNF. *Cytokine* 1989; **1:** 2–13.

24 Gimbrone MA Jr, Obin MS, Brock AF, Luis EA, Hass PE, Hebert CA *et al.* Endothelial interleukin-8: a novel inhibitor of leukocyte–endothelial interactions. *Science* 1989; **246:** 1601–3.

25 Sekido N, Mukaida N, Harada A, Nakanishi I, Watanabe Y, Matsushima K. Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8. *Nature* 1993; **365:** 654–7.

26 Huber AR, Kunkel SL, Todd RF III, Weiss SJ. Regulation of transendothelial neutrophil migration by endogenous interleukin-8. *Science* 1991; **254:** 99–102.

27 Baggiolini M. Novel aspects of inflammation: interleukin-8 and related chemotactic cytokines. *Clin Investig* 1993; **71:** 812–14.

28 Welbourn CR, Goldman G, Paterson IS, Valeri CR, Shepro D, Hechtman HB. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. *Br J Surg* 1991; **78:** 651–5.

29 Cavanagh SP, Gough MJ, Homer-Vanniasinkam S. The role of the neutrophil in ischaemia–reperfusion injury: potential therapeutic interventions. *Cardiovasc Surg* 1998; **6:** 112–18.

30 Froon AH, Greve JW, Van der Linden CJ, Buurman WA. Increased concentrations of cytokines and adhesion molecules in patients after repair of abdominal aortic aneurysm. *Eur J Surg* 1996; **162:** 287–96.

31 Raijmakers PG, Groeneveld AB, Rauwerda JA, Schneider AJ, Teule GJ, Hack CE *et al.* Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. *Am J Respir Crit Care Med* 1995; **151:** 698–705.

32 Hamano K, Gohra H, Noda H, Katoh T, Fujimura Y, Zempo N *et al.* Increased serum interleukin-8: correlation with poor prognosis in patients with postoperative multiple organ failure. *World J Surg* 1998; **22:** 1077–81.

33 Rot A, Hub E, Middleton J, Pons F, Rabeck C, Thierer K *et al.* Some aspects of IL-8 pathophysiology. III: Chemokine interaction with endothelial cells. *J Leukoc Biol* 1996; **59:** 39–44.

34 Tan P, Luscinskas FW, Homer-Vanniasinkam S. Cellular and molecular mechanisms of inflammation and thrombosis. *Eur J Vasc Endovasc Surg* 1999; **17:** 373–89.

35 Moore KW, O'Garra A, de Waal Malefyt R, Vieira P, Mosmann TR. Interleukin-10. *Annu Rev Immunol* 1993; **11:** 165–90.

36 Cassatella MA. The neutrophil: one of the cellular targets of interleukin-10. *Int J Clin Lab Res* 1998; **28:** 148–61.

37 Hess PJ, Seeger JM, Huber TS, Welborn MB, Martin TD, Harward TR *et al.* Exogenously administered interleukin-10 decreases pulmonary neutrophil infiltration in a tumor necrosis factor-dependent murine model of acute viral ischemia. *J Vasc Surg* 1997; **26:** 113–18.

38 Friedman G, Jankowski S, Marchant A, Goldman M, Kahn RJ, Vincent JL. Blood interleukin 10 levels parallel the severity of septic shock. *J Crit Care* 1997; **12:** 183–7.

39 Haupt W, Zirngibl H, Stehr A, Riese J, Holzheimer RG, Hohenberger W. Tumour necrosis factor-alpha and interleukin-10 production in septic patients and the regulatory effect of plasma. *Eur J Surg* 1999; **165:** 95–100.

40 Holmberg A, Bergqvist D, Westman B, Siegbahn A. Cytokine and fibrinogen response in patients undergoing open abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 1999; **17:** 294–300.

41 Oldenburg HA, Burress Welborn M, Pruitt JH, Boelens PG, Seeger JM, Martin TD *et al.* Interleukin-10 appearance following thoraco-abdominal and abdominal aortic aneurysm repair is associated with the duration of visceral ischaemia. *Eur J Vasc Endovasc Surg* 2000; **20:** 169–72.

42 Formigli L, Lombardo LD, Adembri C, Brunelleschi S, Ferrari E, Novelli GP. Neutrophils as mediators of human skeletal muscle ischemia–reperfusion syndrome. *Hum Pathol* 1992; **23:** 627–34.

43 Thompson MM, Nasim A, Sayers RD, Thompson J, Smith G, Lunec J *et al.* Oxygen free radical and cytokine generation during endovascular and conventional aneurysm repair. *Eur J Vasc Endovasc Surg* 1996; **12:** 70–5.

Association of Surgeons

Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre

K. Cassar, D. J. Godden* and J. L. Duncan

Department of Surgery, Raigmore Hospital and *Highlands and Islands Health Research Institute, Inverness, UK
Correspondence to: Mr J. L. Duncan, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, UK (e-mail john.duncan@raigmore.scot.nhs.uk)

Background: Ruptured abdominal aortic aneurysm (RAAA) carries a high community mortality. Raigmore Hospital, Inverness serves Highland Region, an area the size of Wales with a population of 204 000. The aim of this retrospective review was to determine the community mortality and hospital mortality rates from RAAA in Highland Region and to assess whether distance travelled had any significant impact on survival.

Methods: Data were retrieved from hospital records, the Registrar General for Scotland and the Information and Statistics Division of the National Health Service in Scotland about patients diagnosed with RAAA between 1992 and 1999.

Results: Of 198 patients with RAAA, 131 (66 per cent) were transferred to Raigmore Hospital while the other 67 (34 per cent) died in a community hospital or at home. Of those reaching Raigmore 109 (83 per cent) had surgery, of whom 65 (60 per cent) survived. The overall community mortality rate was 67 per cent while the hospital mortality rate was 50 per cent. The hospital and community mortality rates for patients living within 50 miles of Raigmore Hospital were 60 and 67 per cent respectively, compared with 26 and 68 per cent for those living more than 50 miles away.

Conclusion: Distance from Raigmore Hospital had no significant impact on community mortality from RAAA.

Paper accepted 27 May 2001

British Journal of Surgery 2001, 88, 1341–1343

Introduction

Ruptured abdominal aortic aneurysm (RAAA) carries a community mortality rate of 80 per cent or more[1–3]. For those who reach the operating theatre, the mortality rate is between 49 and 70 per cent[4–7]. Although one report from the state of Maryland, USA[8] claims a decline in statewide operative mortality rate from 59 per cent in 1990 to 43 per cent in 1995 there has been little improvement in results over several decades. Raigmore Hospital is a district general hospital in Inverness, Scotland serving Highland Region. This is a very sparsely populated area approximately the size of Wales or Belgium. Five general surgeons operate on patients with RAAA, only one of whom has a major vascular interest. The aim of this study was to determine the community mortality and hospital mortality rates for RAAA in Highland Region and to assess whether the distance travelled had any impact on survival.

Patients and methods

Data were retrieved from the Hospital Records Department database for all patients admitted to Raigmore Hospital with RAAA (International Classification of Disease 1975 Revision 441·3; I71·3) between 1 January 1992 and 31 December 1999. Data were also retrieved from the operating theatre records for all patients who underwent emergency abdominal aortic aneurysm repair for rupture (Office of Population, Censuses and Surveys 4 codes L18·4, L18·6, L48·3) in the same interval. Data from both sources were compared. The day of admission, the source of transfer, the operative procedure and the outcome were obtained. Patients who died from a RAAA between 1992 and 1999 but did not reach hospital were identified from records of the Registrar General for Scotland. These data were cross-checked with information from the Information and Statistics Division of the National Health Service in Scotland, which also provided data about patients diagnosed and treated in the community hospitals but who were not transferred to Raigmore Hospital. Accurate demographic data were available for the population living within 30 miles of Inverness and beyond 30 miles of Inverness. The hospital mortality refers to patients who were admitted to Raigmore Hospital with a diagnosis of RAAA and were not discharged alive. The operative mortality refers to patients who underwent emergency abdominal aortic aneurysm repair for RAAA and who were not discharged alive. The community mortality refers to all patients who died from RAAA, including those who were admitted to Raigmore Hospital.

Results

Between 1992 and 1999, 198 RAAAs were diagnosed in Highland Region. The population of Highland in 1997 was 204 004, giving an incidence of 12·1 per 100 000 per year. The incidence for people living within 30 miles of Inverness was 8·4 per 100 000 per year compared with 15·7 per 100 000 per year for people living beyond 30 miles. Of these, 131 patients were admitted to Raigmore Hospital. The remaining 67 patients were not transferred to Raigmore Hospital; 35 died in a community hospital and 32 died at home. A further 66 of the 131 patients transferred to Raigmore Hospital died, giving a community mortality rate of 67 per cent (133 of 198).

Among the 67 patients who died outside Raigmore Hospital, there were 34 men and 33 women of mean age 75 (range 56–93) years; the mean age for women was 78 years while for men it was 73 years.

Of the 131 patients admitted to Raigmore Hospital, 105 patients (80 per cent) were men and 26 (20 per cent) were women. Twenty-two patients did not have surgery either because of poor medical condition or because they refused. The mean age in this group was 80 years. Some 109 patients (83 per cent) had surgery; their mean age was 74 years. Sixty-five (60 per cent) of these patients survived aneurysm repair and were discharged from hospital. The operative mortality rate was 40 per cent and the hospital mortality rate was 50 per cent (*Fig. 1*). The hospital mortality rate was 50 per cent (52 of 105) in men and 54 per cent (14 of 26) in women. The consultant vascular surgeon performed 41 (38 per cent) of these operations; the remainder were performed equally by the other four surgeons. The operative mortality rate for patients treated by the vascular surgeon was 46 per cent (19 of 41).

Fifteen patients did not normally live in Highland. Of the remaining 116 patients who reached Raigmore Hospital, 58 (50 per cent) had travelled less than 25 miles, 23 (20 per cent) travelled between 25 and 50 miles, 18 (16 per cent) travelled between 51 and 75 miles, and 17 (15 per cent) travelled more than 75 miles (*Table 1*). Half the patients travelled more than 25 miles and almost one-third travelled more than 50 miles to Raigmore Hospital.

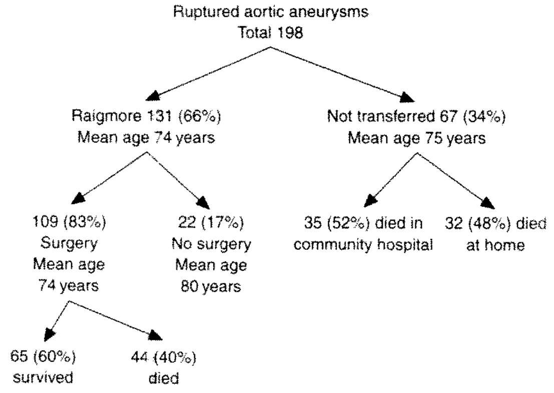


Fig. 1 Ruptured abdominal aortic aneurysms in Highland Region, 1992–1999

Table 1 Outcome of patients admitted to Raigmore Hospital related to distance travelled

Distance travelled (miles)	Survived	Died	Total
< 25	23 (40)	35 (60)	58
25–50	9 (39)	14 (61)	23
51–75	13 (72)	5 (28)	18
> 75	13 (76)	4 (24)	17
Total	58 (50)	58 (50)	116

Values in parentheses are percentages

The hospital mortality rate was 60 per cent in patients who travelled less than 25 miles, the same as that for patients who travelled between 25 and 50 miles (61 per cent). For those who travelled 51–75 miles the hospital mortality rate was 28 per cent and for those who travelled more than 75 miles it was 24 per cent. The decrease in mortality rate with increasing distance travelled was statistically significant ($P = 0{\cdot}008$, χ^2 test). The hospital mortality rate in patients within 50 miles was 60 per cent compared with 26 per cent in those who travelled more than 50 miles ($P < 0{\cdot}001$). However, the community mortality rate in patients who lived within 50 miles of Raigmore Hospital (67 per cent) was the same as that for those living beyond 50 miles (68 per cent).

Discussion

This study shows that both the community (67 per cent) and hospital mortality (50 per cent) rates in a remote and rural area, where a significant proportion of patients live more than 25 miles away from the main hospital, were similar to those in urban areas reported in the literature. The operative mortality rate at Raigmore Hospital (40 per cent) also compares favourably with other studies[3,5–7], even though the hospital does not have continuous vascular surgical cover.

A difference in mortality rate between men and women, as reported by Semmens *et al.*[9] from Western Australia, was also noted in the present study. Although the hospital mortality rate was similar for men (50 per cent) and women (54 per cent), the community mortality rate was higher for women (80 *versus* 62 per cent). A disproportionate number of women (33 of 67) died in the community without being referred to Raigmore Hospital. One reason for this is that rupture occurs later in women; the mean age of women who died in the community was 78 years, compared with 73 years in men. Twenty-nine of 33 women who were not referred to Raigmore Hospital were aged 70 years or more.

This study showed that the distance from the hospital had no significant impact on community mortality. Previous studies have shown similarly that the hospital mortality rate decreases with increasing distance travelled, although these studies looked at urban areas with shorter distances[10,11]. Unfortunately there were insufficient data to assess whether the time interval between diagnosis and arrival at Raigmore Hospital was related to outcome in the present study. It has been presumed that preselection of 'good-risk' patients for transfer over longer distances was the explanation for this lower mortality rate. The geographical location of Raigmore Hospital and the large area that it serves has allowed a study of the effect of long distances travelled. In the present study the hospital mortality rate was lower for those travelling longer distances but the community mortality rate was almost identical. This implies that a greater proportion of patients with a poor prognosis who had a RAAA within 50 miles of Raigmore Hospital were being referred than those beyond 50 miles.

The overall incidence of RAAA in Highland Region was 12·1 per 100 000 per year. The incidence for subjects within 30 miles of Raigmore Hospital was 8·4 per 100 000 per year whereas beyond 30 miles this was 15·7 per 100 000 per year. The marked difference between the two areas initially suggested that the reason for the increased incidence of RAAA in remote areas was that fewer aortic aneurysms were being repaired electively in patients coming from beyond 30 miles. The figures, however, showed that the proportion of patients who had elective aneurysm repair was actually higher for the area beyond 30 miles of Inverness. Another possible explanation was that the proportion of elderly people (especially men) was higher in the remote areas. However, the proportion of people above retirement age living within 30 miles of Raigmore hospital was 17 per cent compared with 18 per cent for the area beyond 30 miles. Among the population above retirement age, 50 per cent were men within 30 miles of Raigmore compared with 55 per cent beyond 30 miles. The minimal differences in age and sex distribution could not therefore explain the difference in the incidence of RAAA. An alternative explanation is that the number of patients per general practitioner is lower in the remote areas than it is within 30 miles of Inverness. General practitioners with a lower patient load are more likely to have met and known the patient before the onset of acute symptoms and may therefore be more likely to make the correct diagnosis. They may also be more selective in referring patients with RAAA as they are more likely to be aware of their premorbid state and quality of life.

References

1 Hak E, Balm R, Eikelboom BC, Akkersdijk GJM, van der Graaf Y. Abdominal aortic aneurysm screening: an epidemiological point of view. *Eur J Vasc Endovasc Surg* 1996; **11:** 270–8.

2 Choksy SA, Wilmink AB, Quick CR. Ruptured abdominal aortic aneurysm in the Huntingdon district: a 10-year experience. *Ann R Coll Surg Engl* 1999; **81:** 27–31.

3 Kantonen I, Lepantalo M, Brommels M, Luther M, Salenius JP, Ylonen K. Mortality in ruptured abdominal aortic aneurysms. The Finnvasc Study Group. *Eur J Vasc Endovasc Surg* 1999, **17:** 208–12.

4 Basnyat PS, Biffin AH, Moseley LG, Hedges AR, Lewis MH. Mortality from ruptured abdominal aortic aneurysm in Wales. *Br J Surg* 1999; **86:** 765–70.

5 Martinez R, Garces D, Podeur L, Abdel Aal K, Laffon M, Castellani L. Ruptured abdominal aortic aneurysm. A ten year experience. *J Cardiovasc Surg* 1997; **38:** 1–6.

6 Bradbury AW, Makhdoomi KR, Adam DJ, Murie JA, Jenkins AM, Ruckley CV. Twelve-year experience of the management of ruptured abdominal aortic aneurysm. *Br J Surg* 1997; **84:** 1705–7.

7 Milner QJ, Burchett KR. Long-term survival following emergency abdominal aortic aneurysm repair. *Anaesthesia* 2000; **55:** 432–5.

8 Dardik A, Burleyson GP, Bowman H, Gordon TA, Williams GM, Webb TH *et al.* Surgical repair of ruptured abdominal aortic aneurysms in the state of Maryland: factors influencing outcome among 527 recent cases. *J Vasc Surg* 1998; **28:** 413–20.

9 Semmens JB, Norman PE, Lawrence-Brown MM, Holman CD. Influence of gender on outcome from ruptured abdominal aortic aneurysm. *Br J Surg* 2000, **87:** 191–4.

10 Barros D'Sa AAB. Optimal travel distance before ruptured aortic aneurysm repair. In: Greenlagh RM, Mannick JA, Powell JT, eds. *The Cause and Management of Aneurysms.* London: WB Saunders, 1990: 409–31.

11 Adam DJ, Mohan IV, Stuart WP, Bain M, Bradbury AW. Community and hospital outcome from ruptured abdominal aortic aneurysm within the catchment area of a regional vascular surgical service. *J Vasc Surg* 1999; **30:** 922–8.

Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note)

B. Neary, B. Whitman, C. Foy, B. P. Heather and J. J. Earnshaw

Gloucestershire Vascular Group, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK
Correspondence to: Mr J. J. Earnshaw (e-mail: earnshaw@rudford.demon.co.uk)

Paper accepted 4 July 2001

Introduction

The Physiological and Operative Severity Score for the enUmeration of Morbidity and mortality (POSSUM) scoring system was developed in 1991 by Copeland *et al.*[1] to enable outcome prediction for surgical operations. It has two components: a physiology score including 14 variables, where weightings are given for degree of cardiac, respiratory and biochemical dysfunction, and an operative score including six variables, where the score relates to the severity of the operation. A recent prospective audit of 1345 arterial operations showed that the physiological score alone also predicted outcome[2]. Adding the operative data did not increase the predictive power of the score. The aim of the present study was to determine whether POSSUM physiology scoring might be valuable in patients having a non-surgical procedure.

Intra-arterial thrombolysis is an established option for selected patients with acute leg ischaemia, but it carries a significant risk of death or complication[3]. Data on all patients who had intra-arterial thrombolysis for acute leg ischaemia in Gloucester since 1992 have been collected prospectively and included in the National Audit of Thrombolysis for Acute Leg Ischaemia (NATALI) database[4]. In this study, the case records of these patients were reviewed and a retrospective POSSUM physiology score was calculated and then related to outcome.

Patients and methods

Since 1992, 149 consecutive patients have undergone 176 events of intra-arterial thrombolysis for acute leg ischaemia in Gloucestershire Royal Hospital. Their clinical details and outcome data have been recorded prospectively on the NATALI database using outcome definitions reported in detail previously[4]. The 30-day event-related outcome for the entire group was limb salvage in 121 cases (69 per cent), amputation in 21 (12 per cent) and death in 34 (19 per cent). Twenty-five of these patients had lysis for subcritical ischaemia and were therefore excluded from the study. Case records of the remaining patients were reviewed and POSSUM physiology scores calculated retrospectively from test results filed in the records as close as possible to the time of thrombolysis. Missing data variables scored 1. It was not possible to retrieve the case records of 23 patients despite searching archived and microfilm records. This left 121 events of thrombolysis for analysis. Each event was analysed separately.

Statistical comparison was carried out with the χ^2 test to detect any trend in the actual mortality according to predicted mortality groupings. Predicted mortality was calculated by applying the Copeland equation to the recorded POSSUM physiology scores.

Results and conclusion

The study group comprised 100 patients who had 121 events of intra-arterial thrombolysis for acute critical leg ischaemia between 1992 and 1999. There were 53 men and 47 women of median age at the time of treatment of 72 (range 44–91) years. One hundred and thirteen thrombolytic treatments were performed using tissue plasminogen activator, but early in the series eight patients received low-dose intra-arterial streptokinase.

The initial results after thrombolysis, as judged by the radiologist, were complete lysis in 40 per cent, partial lysis in 23 per cent, lysis but no run-off in 17 per cent and no lysis in 20 per cent. After 30 days the final result was limb salvage in 85 (70 per cent), amputation in nine (7 per cent) and death in 27 (22 per cent). In addition, a number of patients developed complications, including major haemorrhage in eight (7 per cent), groin haematoma in seven (6 per cent), reperfusion injury in four (3 per cent) and distal embolization in one (1 per cent). There was a significant association between the mortality rate after intra-arterial thrombolysis and the POSSUM physiology score. The mortality rate increased from 0 of 44 patients in the lowest risk category (mortality risk of 0–4 per cent) to seven of eight in the highest risk category (mortality risk greater than 60 per cent) ($P < 0.001$, χ^2 test for trend) (*Table 1*).

This study has shown that POSSUM physiology scoring can predict death after a non-surgical intervention for acute leg ischaemia. This might allow meaningful case-mix analysis and comparative audit of other endovascular and non-surgical interventions. Intra-arterial thrombolysis was chosen for study because it is a risky procedure with a high complication rate. Thrombolysis is most effective for occlusions of short duration and for occluded vascular grafts. The severity of the ischaemia is also an important determinant of outcome for the leg. In the present study, POSSUM physiology scoring, previously validated in

Table 1 Stratification of deaths after 121 events of peripheral thrombolysis using Physiological and Operative Severity Score for the enUmeration of Morbidity and mortality (POSSUM) physiology scores

	Mortality risk (%)					
	0–4	4–10	10–25	25–60	> 60	Total
No. of lysis events	44	39	24	6	8	121
No. of deaths	0	6	12	2	7	27

$P < 0{\cdot}001$ (χ^2 test for trend)

arterial surgery[2], was highly effective in predicting death after intra-arterial thrombolysis.

One limitation of the study is its retrospective nature, with problems of note retrieval and data extraction. However, most thrombolytic events for critical ischaemia in the last 10 years were scored, including 27 of 34 resulting in death.

The mortality rate after intra-arterial thrombolysis was higher in Gloucester than in the entire NATALI database[5]. One factor might have been the inclusion of high-risk patients: a number of apparently very high-risk patients (mortality risk greater than 60 per cent) were treated. In retrospect, knowledge of the POSSUM physiology score before thrombolysis might have been useful in pretreatment counselling.

Acknowledgements

The authors thank Boehringer Ingelheim for continued financial support of the NATALI database, and members of the Thrombolysis Study Group for advice and suggestions regarding study design and analysis.

References

1 Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991; **78:** 355–60.

2 Prytherch DR, Ridler BMF, Beard JD, Earnshaw JJ, the Audit and Research Committee of the Vascular Surgical Society of Great Britain and Ireland (VSSGBI). A model for national outcome audit in vascular surgery. *Eur J Vasc Endovasc Surg* 2001; **21:** 477–83.

3 Working Party on Thrombolysis in the Management of Limb Ischemia. Thrombolysis in the management of lower limb peripheral arterial occlusion – a consensus document. *Am J Cardiol* 1998; **81:** 207–18.

4 Braithwaite BD, Ritchie AWS, Earnshaw JJ. NATALI – a model for National Computer Databases in the investigation of new therapeutic techniques. *J R Soc Med* 1995; **88:** 511–15.

5 Braithwaite BD, Whitman B, Foy C, The Thrombolysis Study Group. Outcome analysis of over 1000 episodes of limb ischaemia treated by peripheral thrombolysis. *Br J Surg* 2001; **88:** 618 (Abstract).

Association of Surgeons

Diagnosis and management of a mediastinal leak following radical oesophagectomy

S. M. Griffin, P. J. Lamb, S. M. Dresner, D. L. Richardson and N. Hayes

Northern Oesophago-Gastric Cancer Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK
Correspondence to: Professor S. M. Griffin, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK
(e-mail: s.m.griffin@ncl.ac.uk)

Background: The aim of this study was to evaluate the diagnosis, management and outcome of mediastinal leaks following radical oesophagectomy with a stapled intrathoracic anastomosis.

Methods: Some 291 consecutive patients underwent two-phase subtotal oesophagectomy with gastric interposition for malignancy. Patients with clinical suspicion of a leak were investigated with contrast radiology and flexible upper gastrointestinal endoscopy.

Results: Nineteen patients (6·5 per cent) developed a proven mediastinal leak at a median of 8 (range 3–30) days following surgery. Contrast radiology and flexible upper gastrointestinal endoscopy identified that 13 patients had an isolated leak from the oesophagogastric anastomosis and two had widespread leakage secondary to gastrotomy-line dehiscence. Endoscopy revealed a further four patients with gastric necrosis in whom contrast radiology was normal. In six patients the diagnosis of leakage followed an apparently normal routine contrast examination on day 5–8. All 13 isolated anastomotic leaks were managed non-operatively with targeted mediastinal drainage, intravenous antibiotics and antifungal therapy, nasogastric decompression and enteral nutrition; the mortality rate was 15 per cent (two of 13). Patients with gastrotomy dehiscence or gastric necrosis had a more severe clinical picture; they were managed with repeat thoracotomy and either revision of the conduit or resection and exclusion. Despite early intervention four of the six patients died.

Conclusion: Routine postoperative contrast radiology cannot be recommended. On clinical suspicion of a leak patients require both contrast radiology and endoscopic evaluation. Isolated anastomotic leaks can be managed successfully with non-operative treatment, whereas more extensive leaks from the gastric conduit require revisional surgery which carries a high mortality rate.

Paper accepted 8 July 2001

British Journal of Surgery 2001, **88**, 1346–1351

Introduction

Intrathoracic leakage after oesophagectomy is a devastating complication responsible for 25–50 per cent of postoperative deaths[1,2]. This significant mortality rate has driven the attempts to identify aetiological factors. Despite developments in the understanding of this major complication, there is no consensus on the optimal site and technique for oesophagogastric anastomosis. There also remains controversy regarding the detection and management of mediastinal leaks after oesophagectomy.

Many authors continue to use routine postoperative contrast radiology to assess anastomotic integrity after oesophagectomy[3], despite criticism of the clinical value of this as a routine investigation[4]. Most surgeons advocate non-operative treatment for small, localized leaks, but the indications, timing and nature of operative intervention remain unclear. This continuing controversy results partly from an initial failure to identify the true cause and extent of any leak. Isolated leakage from the oesophagogastric anastomosis, leakage from the gastrotomy line and gastric ischaemia are often falsely regarded as a single entity. However, there are significant differences in the degree of contamination, clinical features and management. The aim of this study was to review the method of diagnosis, management and outcome in patients who had a postoperative mediastinal leak following radical oesophagectomy with a stapled intrathoracic anastomosis.

Patients and methods

From 1 April 1990 to 30 September 2000, 291 consecutive patients had two-phase subtotal oesophagectomy with two-field lymphadenectomy for carcinoma of the oesophagus or gastro-oesophageal junction in this institution. The median age was 64 (range 30–78) years with a male to female ratio of 3 : 1. Data were collected prospectively on a Microsoft Access (Microsoft Corporation, Redmond, Washington, USA) database, and analysed to determine the incidence, management and outcome of patients who developed a postoperative mediastinal leak. A clinicopathological comparison was made with those patients who did not develop a mediastinal leak to seek aetiological factors. Statistical significance was determined by χ^2 analysis or Student's t test and $P < 0.05$ was considered statistically significant.

Surgical technique

The detailed resection technique is described elsewhere[5]. In brief, in all patients the stomach was used for reconstruction based on a vascular pedicle of the right gastric and gastroepiploic arteries. A pyloroplasty was carried out routinely to facilitate postoperative gastric emptying. The stapled oesophagogastric anastomosis was performed at the apex of the thorax and placed at the high point of the fundus away from the gastrotomy line so as not to compromise the blood supply. After stapling the doughnuts were examined for completeness and the anastomosis was inspected from inside for integrity. A nasogastric tube was introduced and the gastrotomy resection line was stapled and oversewn.

Diagnosis and classification of mediastinal leakage

The 139 patients operated on before May 1997 underwent a routine contrast swallow examination between 5 and 8 days after operation using water-soluble contrast, followed by barium if no leak was identified. Routine contrast examinations were then abandoned, as it was perceived that patients were presenting clinically with a leak following normal contrast radiology, and two patients developed aspiration bronchopneumonia after a routine examination. For the subsequent 152 patients unlimited oral fluid intake was commenced on day 5 and diet was introduced on day 7. A contrast examination was performed only if there were intraoperative technical difficulties in performing the anastomosis. If the postoperative recovery was complicated or there was clinical suspicion of a leak patients were investigated by contrast radiology together with flexible upper gastrointestinal endoscopy.

The diagnosis of leak was made by observing extravasation during a contrast swallow examination or by the appearance of a defect on flexible upper gastrointestinal video endoscopy. Gastric necrosis was considered to be present when there was unequivocal necrotic damage extending deep to the mucosa on endoscopy. Based on these investigations, mediastinal leaks were classified as originating from either the oesophagogastric anastomosis or the gastrotomy line, or resulting from necrosis of the gastric conduit.

Management policy for mediastinal leakage

The policy was for initial non-operative treatment of patients with true oesophagogastric anastomotic leakage without evidence of gastric necrosis. This included absolute avoidance of oral intake with enteral nutrition, mediastinal and chest drainage, intravenous antimicrobials and full supportive treatment. In the presence of gastric necrosis or a leak from the gastrotomy suture line, early reoperation was performed and tailored to each individual patient.

Results

Diagnosis and classification of mediastinal leakage

Mediastinal leakage occurred in 19 patients (6·5 per cent), 16 men and three women, with a median age of 64 (range 46–78) years. Leaks were diagnosed at a median of 8 (range 3–30) days following surgery. Sixteen of the 19 patients presented symptomatically, nine patients with localized chest symptoms, one patient with gastrointestinal haemorrhage and six patients with systemic sepsis (*Table 1*).

During the interval in which routine postoperative contrast radiology was performed, ten (7·2 per cent) of 139 patients were diagnosed with a mediastinal leak. A routine contrast swallow identified only one of these leaks; three patients were investigated for symptoms before the routine contrast swallow and six leaks presented in patients who previously had an apparently normal routine postoperative contrast swallow.

In the cohort who did not undergo routine contrast radiology nine (5·9 per cent) of 152 patients developed a leak. Two leaks were asymptomatic and were identified by a scheduled contrast examination performed following intraoperative anastomotic difficulty. Six leaks were identified from a group of 20 patients who underwent contrast radiology for clinical suspicion of leakage. One further leak was diagnosed by endoscopic evaluation alone while the patient was ventilated in the intensive therapy unit.

Based on contrast radiography and the endoscopic appearance, 13 leaks originated from the oesophagogastric anastomosis, two from the gastrotomy line and four secondary to necrosis of the gastric conduit. A contrast swallow accurately demonstrated a leak at the time of symptoms in all 13 patients with a true oesophagogastric anastomotic leak and in both cases of leakage secondary to gastrotomy-line dehiscence. However, when gastric necrosis was the underlying problem, no leaks were detected by contrast examination (*Table 1*). The correct diagnosis was made in all four patients by flexible upper gastrointestinal video endoscopy and confirmed at repeat thoracotomy. During the study interval endoscopic examination excluded a mediastinal leak in a further 19 patients with postoperative complications in the intensive therapy unit.

Aetiological factors

Technical factors

Intraoperative difficulties were documented in five patients who developed a leak. Gastric mobilization was complicated in two patients, in one by damage to the right gastric artery and in the other owing to a previous gastroenterostomy for peptic ulcer disease. In three patients a mucosal tear developed in the oesophageal wall during the anastomosis. In all these the stomach and anastomosis appeared well vascularized and integral at the end of the procedure.

The median diameter of staple gun used in the subgroup of patients who developed a leak was 28 (range 21–31) mm, the same as for the other patients. Histopathological examination revealed a positive resection margin in one patient who developed a leak (*Table 2*). There was no statistically significant difference in the tumour node metastasis stage of disease between patients who developed a leak and those who did not.

Patient factors

There was no association between the development of a leak and a past history of ischaemic heart disease or diabetes, cigarette smoking, treatment with neoadjuvant chemoradiotherapy or low body mass index (*Table 2*).

Management

Management was based on a multidisciplinary approach with input from the oesophagogastric surgeon, intensivist, interventional radiologist, physiotherapist, dietician and nursing staff. Patients were managed in the intensive therapy unit (11 of 19) or surgical high-dependency unit (eight). Non-operative therapy was rapidly instituted for the 13 patients with isolated oesophagogastric anastomotic leakage to minimize mediastinal and pleural contamination. A nasogastric tube was left *in situ* or reintroduced under radiological or endoscopic control. Perianastomotic and pleural drainage was performed via existing chest drains in four patients and by insertion of drains under computed

Table 1 Diagnosis, management and outcome of mediastinal leaks after oesophagectomy

Type of leak	Symptoms at diagnosis	Seen on contrast swallow	Seen on endoscopy	Treatment	In-hospital death
Anastomotic ($n = 13$)	Chest 9 Gastrointestinal bleed 1 None 3	13 of 13	10 of 13*	Non-operative 13	2 of 13
Gastrotomy line ($n = 2$)	Systemic sepsis 2	2 of 2	2 of 2	Revision of gastrotomy 2	1 of 2
Gastric necrosis ($n = 4$)	Systemic sepsis 4	0 of 3†	4 of 4	Refashioning 2 Resection and exclusion 2	3 of 4

*Three patients did not have endoscopy; †one patient did not have contrast swallow (ventilated)

Table 2 Risk factors for developing a mediastinal leak

	Mediastinal leak ($n = 19$)	No mediastinal leak ($n = 272$)	χ^2	P
Median size of staple gun (mm)	28	28		n.s.
Positive resection margin	1 (5)	11 (4)		n.s.
Ischaemic heart disease/diabetes	7 (37)	85 (31)	0·26	n.s.
Neoadjuvant treatment	2 (11)	13 (5)	1·20	n.s.
Smoking	11 (58)	129 (47)	0·80	n.s.
Body mass index	23·6	24·5		n.s.

Values in parentheses are percentages. n.s., not significant. *t* test tomographic or ultrasonographic guidance in nine patients. Five patients subsequently required further radiologically guided drainage of a loculated collection. Broad-spectrum intravenous antibiotics and antifungal therapy were given. Enteral nutrition was provided either via an endoscopically placed fine-bore nasojejunal tube (seven of 13) or a feeding jejunostomy (six). All patients received intensive chest physiotherapy and one patient required a tracheostomy for respiratory support. None of these 13 patients subsequently underwent reoperation.

Two patients had evidence of leakage from the gastrotomy line, one with necrosis visible at endoscopy. After resuscitation both underwent thoracotomy with refashioning of the gastrotomy. The four patients with gastric necrosis had the most severe clinical picture and all needed reoperation. Two had refashioning of the anastomosis with the insertion of a T tube in one patient to form a controlled oesophagocutaneous fistula. The aim of this is to stimulate formation of a mature tract; the T tube can be removed after 3 weeks if oral and T-tube contrast studies are satisfactory. Two further patients with more extensive necrosis had resection of the gastric conduit and formation of a cervical oesophagostomy and gastrostomy.

Outcome

The in-hospital mortality rate was 5·5 per cent (16 of 291) overall and 32 per cent (six of 19) for patients who developed a mediastinal leak. Two of 13 patients with oesophagogastric anastomotic leakage died, one from respiratory complications secondary to broncho-oesophageal fistulation (day 17) and one from haemorrhage from the fistula tract (day 19). One of the two patients with a gastrotomy dehiscence died from haemorrhage from the fistula tract (day 26). Three of four patients with necrosis of the gastric conduit died from multiple organ failure (days 10, 14 and 34), following revision of the anastomosis in two patients, and resection and exclusion in the third. The median hospital stay for the 13 patients who survived was 42 (range 13–99) days, significantly longer than that of 14 (range 8–222) days for all other patients ($P < 0.05$).

Discussion

The overall mediastinal leak rate reported in the present study is 6·5 per cent (19 of 291), comprising 4·5 per cent from the oesophagogastric anastomosis, 0·7 per cent from the gastrotomy line and 1·4 per cent as a result of necrosis of the gastric conduit. This is comparable to recently reported rates of 3·5 and 7·8 per cent following oesophagectomy with a stapled intrathoracic anastomosis[1,3], although no breakdown with respect to the type of leak was provided in these studies. A study of 159 patients from Hong Kong[6] reported a clinical leak rate of 3·8 per cent including 2·5 per cent anastomotic leaks and 1·3 per cent secondary to gastric necrosis, proportions similar to the present series. Some of these reports identified underlying intraoperative factors in the aetiology of the majority of subsequent leaks[3,6]. This was not demonstrated in the present study in which such factors were identified in only five operations, and no patient characteristic was significantly associated with leakage. Although there is controversy regarding the optimal site and technique of anastomosis, a number of studies have detected no difference in leak rate between thoracic or cervical, and handsewn or stapled anastomoses[2,7,8]. Nevertheless stapled intrathoracic anastomoses have been shown to decrease operating time and intraoperative blood loss[8] and the present results confirm that they can be performed with a low leak rate.

Despite recognition of the limitations of routine contrast radiology after oesophagectomy[1,3,4,6], this investigation is still used widely in clinical practice. A very low rate of subclinical leakage was detected using this technique in the early part of the present study (one of 139 patients). During this interval two patients developed aspiration pneumonia and six patients presented clinically with a leak following an apparently normal contrast swallow. It is not known whether these were true late leaks or if they were missed during the original examination despite the use of both water-soluble contrast and barium by a specialist radiologist. Subsequently routine contrast swallows were not performed and instead an active approach towards excluding leaks based on clinical suspicion was adopted, resulting in a high diagnostic rate from the limited number of examinations carried out.

Endoscopic assessment has been regarded as a hazardous investigation after oesophagectomy owing to concerns regarding potential disruption of the oesophagogastric anastomosis. In the hands of an experienced endoscopist using minimal air insufflation it does not cause further damage to an area of leakage, and can provide invaluable clinical information on the precise site and cause. In particular, it can identify the presence and extent of any gastric conduit necrosis which will not be detected by a contrast examination. Endoscopy can also be performed on ventilated patients in the intensive therapy unit and is vital to exclude or confirm a leak. It also facilitates insertion of nasojejunal and nasogastric tubes for feeding and drainage. All patients in this study received enteral nutrition via a nasojejunal tube or feeding jejunostomy; this is associated with fewer septic complications than parenteral nutrition[9].

Rapid diagnosis and early intervention is essential to limit contamination and minimize sepsis. This requires close cooperation and communication between surgeon, intensi-

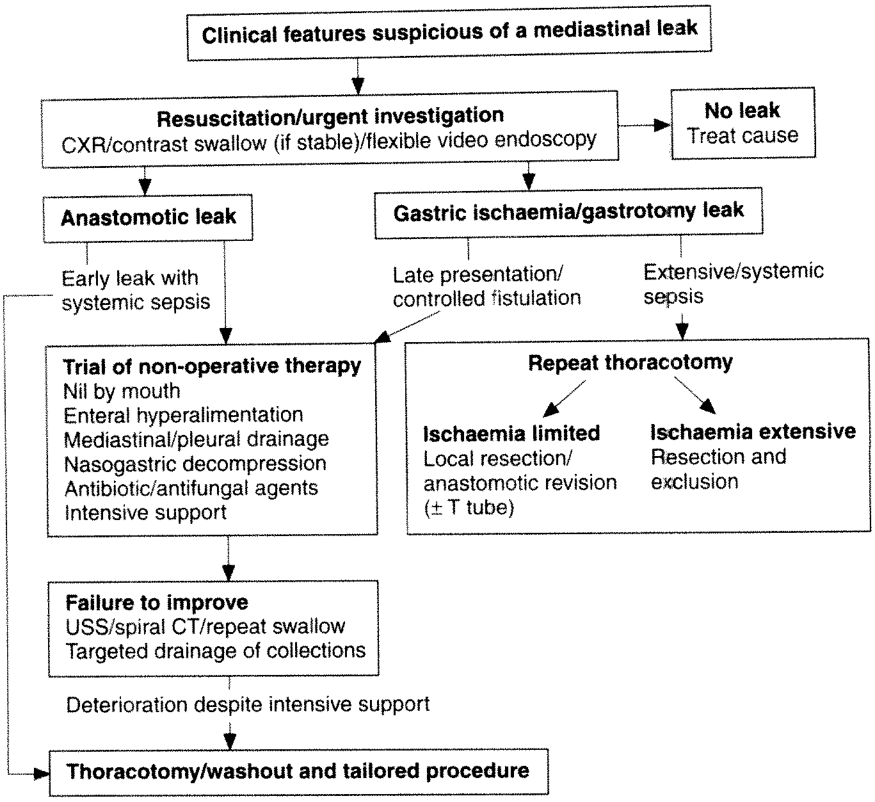

Clinical features suspicious of a mediastinal leak
Resuscitation/urgent investigation
CXR/contrast swallow (if stable)/flexible video endoscopy
No leak
Treat cause
Anastomotic leak
Gastric ischaemia/gastrotomy leak
Early leak with systemic sepsis
Late presentation/ controlled fistulation
Extensive/systemic sepsis
Trial of non-operative therapy
Nil by mouth
Enteral hyperalimentation
Mediastinal/pleural drainage
Nasogastric decompression
Antibiotic/antifungal agents
Intensive support
Repeat thoracotomy
Ischaemia limited
Local resection/ anastomotic revision (± T tube)
Ischaemia extensive
Resection and exclusion
Failure to improve
USS/spiral CT/repeat swallow
Targeted drainage of collections
Deterioration despite intensive support
Thoracotomy/washout and tailored procedure

Fig. 1 Algorithm for the management of patients with a suspected mediastinal leak. CT, computed tomography; CXR, chest radiograph; USS, ultrasound scan

vist and interventional radiologist working within a broad multidisciplinary team. The distinction between true anastomotic leakage, leakage from the gastrotomy line and necrosis of the gastric conduit is often overlooked but there are significant differences in the degree of contamination, clinical presentation and subsequent management. A suggested algorithm for the diagnosis and management of patients with clinical features suggestive of mediastinal leakage is given in *Fig. 1*.

All 13 patients with an isolated anastomotic leak without macroscopic evidence of necrosis were managed non-operatively, resulting in only two deaths. These patients have a lesser degree of mediastinal contamination, but nevertheless require active supportive treatment with continuous monitoring. Adequate mediastinal and pleural drainage is important to reduce septic and respiratory complications. A high index of suspicion must be maintained and patients who fail to improve clinically should be reinvestigated to identify persisting collections. Repeated radiologically guided drainage of loculated collections is often required.

The indications for operative intervention in patients with a mediastinal leak are unclear. Reoperation is clearly indicated for early technical failure leading to a complete breakdown of the anastomosis[10], but this did not occur in the present series. Gastrotomy leaks are associated with a high degree of contamination and both patients in this series underwent revision of the gastrotomy. The presence of gastric necrosis was associated with the most severe clinical picture. Where this was limited, local revision of the conduit and anastomosis was performed; with total gastric necrosis, the stomach was resected and an exclusion procedure was performed. Despite early intervention and aggressive supportive treatment the outcome for patients undergoing reoperation for gastrotomy dehiscence and gastric necrosis was poor; four of the six patients died.

The in-hospital mortality rate for patients who developed a mediastinal leak was 32 per cent (six of 19), comparable to previous series[1,2]. Two per cent of all patients died as a result of mediastinal leakage; however, it should be noted that this accounted for six of the 16 postoperative deaths in this series.

Based on the present results, routine contrast radiology cannot be recommended after oesophagectomy owing to its low diagnosis rate, high false-negative rate and the associated risk of aspiration. Patients with clinical suspicion of a mediastinal leak require urgent investigation by both contrast radiology and endoscopy. Rapid diagnosis and early institution of treatment is essential to minimize sepsis and should involve senior staff working within a multidisciplinary team. Isolated anastomotic leaks can be managed successfully by aggressive non-operative treatment in most patients. For more extensive leaks from the gastric conduit revisional surgery offers the only chance of survival but inevitably carries a high mortality rate.

References

1 Karl RC, Schreiber R, Boulware D, Baker S, Coppola D. Factors affecting morbidity, mortality, and survival in patients undergoing Ivor Lewis esophagogastrectomy. *Ann Surg* 2000; **231:** 635–43.

2 Valverde A, Hay JM, Fingerhut A, Elhadad A. Manual *versus* mechanical esophagogastric anastomosis after resection for carcinoma: a controlled trial. French Association for Surgical Research. *Surgery* 1996; **120:** 476–83.

3 Sauvanet A, Baltar J, Le Mee J, Belghiti J. Diagnosis and conservative management of intrathoracic leakage after oesophagectomy. *Br J Surg* 1998; **85:** 1446–9.

4 Wong J, Cheung H, Lui R, Fan YV, Smith A, Siu KF. Esophagogastric anastomosis performed with a stapler: the occurrence of leakage and stricture. *Surgery* 1987; **101:** 408–15.

5 Griffin SM. Surgery for cancer of the oesophagus. In: Griffin SM, Raimes SA, eds. *Upper Gastrointestinal Surgery*. London. WB Saunders, 1997: 111–44.

6 Paterson IM, Wong J. Anastomotic leakage: an avoidable complication of Lewis–Tanner oesophagectomy. *Br J Surg* 1989; **76:** 127–9.

7 Lam TC, Fok M, Cheung SW, Wong J. Anastomotic complications after esophagectomy for cancer. A comparison of neck and chest anastomoses *J Thorac Cardiovasc Surg* 1992; **104:** 395–400.

8 Craig SR, Walker WS, Cameron EWJ, Wightman AJA. A prospective randomized study comparing stapled with handsewn oesophagogastric anastomoses. *J R Coll Surg Edinb* 1996; **41:** 17–19.

9 Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB *et al* Early enteral feeding, compared with parenteral reduces postoperative septic complications. The results of a meta-analysis. *Ann Surg* 1992; **216:** 172–83.

10 Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *Am J Surg* 1995; **169:** 634–40.

Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer

A. I. Sarela, J. A. Guthrie*, M. T. Seymour†, E. Ride†, P. J. Guillou and D. S. O'Riordain

Academic Unit of Surgery and †Imperial Cancer Research Fund Cancer Medicine Research Centre, School of Medicine, University of Leeds and Departments of Surgery, *Radiology and †Medical Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
Correspondence to: Mr D. S. O'Riordain, Department of Surgery, Adelaide and Meath Hospitals, Tallaght, Dublin 24, Ireland
(e-mail: doriordain@msn.com)

Background: Excision of primary colorectal cancer associated with irresectable synchronous metastases confers high morbidity and mortality with uncertain benefit.

Methods: For patients with incurable stage IV colorectal cancer, minimally symptomatic primary tumours were left *in situ* and 5-fluorouracil-based chemotherapy was administered systemically. Primary tumour-specific complications and survival were monitored.

Results: There were 13 men and 11 women with primary tumours in the right colon (eight), transverse colon (one), sigmoid colon (eight) or rectum (seven). Eleven patients had metastases limited to the liver (liver replacement less than 25 per cent in one, 25–50 per cent in four and more than 50 per cent in six) and 13 patients had extrahepatic disease (lung or peritoneum). Four patients with sigmoid colon tumours developed bowel obstruction, which required an uncomplicated operation in two and deployment of colonic stents in two patients, at 1, 3, 12 and 20 months from diagnosis. Three further patients underwent right hemicolectomy for abdominal pain of uncertain aetiology, with poor symptomatic relief, and another had a potentially curative operation following disease downstaging. The overall median survival was 10·3 months with a 1-year actuarial survival rate of 44 per cent.

Conclusion: A policy to defer resection of minimally symptomatic primary colorectal cancer is associated with a low risk of complications before death from progressive systemic disease.

Paper accepted 2 July 2001

British Journal of Surgery 2001, **88**, 1352–1356

Introduction

In the UK, approximately 34 000 patients have colorectal cancer newly diagnosed each year and up to 20 per cent of these are found to have synchronous distant metastases[1]. Only a highly selected subgroup (20–30 per cent) of such patients with stage IV disease is suitable for resection of hepatic metastases[2]. For the remaining majority, the therapeutic aim is to provide optimal palliation in terms of survival and health-related quality of life. Early surgical literature recommends resection of the primary tumour, irrespective of symptoms, in order to pre-empt potential complications, such as intestinal obstruction, perforation or haemorrhage, and possibly prolong survival[3,4]. More recent reports largely reiterate this recommendation, but suggest non-operative management of the primary tumour selectively for elderly patients[5,6] and those with extensive liver disease[5–7] or diffuse peritoneal metastases[5]. However, colonic resection, even in a non-urgent situation, is associated with a high mortality rate (8 per cent) for patients with stage IV disease[8]. Moreover, postoperative morbidity may delay or even preclude systemic chemotherapy, which is of established value for palliation in such patients[9].

The authors have argued previously that most patients with incurable stage IV colorectal cancer and a minimally symptomatic primary tumour, regardless of age or volume of metastases, are likely to die from progressive systemic disease before the development of any primary tumour-specific complication[10]. The present study examined whether an operation could be safely avoided for such patients.

Patients and methods

Patient selection

Patients with histopathologically proven stage IV colorectal cancer were identified prospectively during 1999 and 2000 at a multidisciplinary meeting of specialist colorectal and liver surgeons, medical oncologists, radiologists and pathologists. Additional patients were identified by retrospective review of a medical oncology database for 1997 and 1998. Staging investigations comprised a minimum of dual-contrast spiral computed tomography (CT) of the abdomen and pelvis, and a chest radiograph. In selected patients, magnetic resonance imaging of the liver and/or pelvis and CT of the chest were also performed. The size and local extent of the primary disease were recorded, as were the presence and extent of disease within local and distant lymph nodes, the liver, lungs and peritoneum. Radiological evidence of intestinal obstruction, and maximal diameters of the caecum and small bowel, were noted.

During each year of this study period, there were approximately 400 patients with newly diagnosed colorectal cancer and up to 100 patients received palliative chemotherapy for advanced colorectal cancer. Patients with primary colorectal cancer and synchronous metastases were included if: (1) they were not candidates for resection of metastatic disease; (2) there were minimal symptoms related to the primary tumour and immediate operation was not required for palliation; and (3) their functional performance status was sufficiently good to receive systemic chemotherapy. Patients with locally advanced primary tumours that appeared irresectable were excluded from the study.

All patients were counselled regarding the potential benefits and risks of non-operative management, and were offered systemic chemotherapy, symptom control measures such as analgesia and laxatives, and psychosocial support. Careful clinical monitoring of complications related to the primary tumour and survival was conducted.

Chemotherapy

Despite the initial intention to treat, three patients did not eventually receive palliative chemotherapy. One patient died owing to rapidly progressive disease before starting chemotherapy; issues surrounding the other two patients are described in the results section. The remaining patients received a modification of the de Gramont regimen[11]. Additionally, three patients received oxaliplatin and another three received irinotecan, for first-line therapy. Response to chemotherapy was monitored by serial CT scans and measurement of serum carcinoembryonic antigen levels. Second-line chemotherapy for progressive disease, following an initial partial response, was administered to seven patients and included oxaliplatin in four cases and irinotecan in three.

Statistical analysis

The biostatistics package SPSS version 9 (SPSS, Chicago, Illinois, USA) was used. Summary statistics are presented as median (interquartile range). Actuarial survival analyses were conducted by the Kaplan–Meier method.

Results

Clinical and radiological characteristics

There were 13 men and 11 women aged 70 (63–74) years. The main presenting symptoms were alteration in bowel habit (nine), weight loss (five), minor rectal bleeding (four), abdominal pain (two), dysuria (two), iron-deficiency anaemia (one) and perforated appendicitis with a non-obstructing tumour in the transverse colon (one). At diagnosis, no patient had clinically or radiologically apparent bowel obstruction or required blood transfusion. Primary tumours were located in the right colon (eight), transverse colon (one), sigmoid colon (eight) or rectum (seven).

At assessment of CT scans, diameter (3·2 (3·0–4·0) cm), length (4·7 (3·0–6·0) cm) and wall thickness (1·5 (1·1–1·9) cm) of the primary tumour were recorded. Infiltration into adjacent fat was noted in ten patients. There was no involvement of small bowel or other adjacent organs. Enlarged lymph nodes were observed at mesenteric or pericolic sites in ten patients (maximum diameter 1·2 (1·0–2·8) cm) and at para-aortic sites in four patients (maximum diameter 2·5 (1·3–3·6) cm). Liver metastases were noted in 22 of 24 patients. The volume of liver parenchyma replaced by tumour was less than 25 per cent in six patients, 25–50 per cent in seven and more than 50 per cent in nine patients. The maximum diameter of liver metastases was 6·0 (3·6–9·3) cm. Lung metastases were present in ten patients. Peritoneal metastases were observed in six patients, with ascites in three and solid peritoneal deposits in five patients. Overall, extrahepatic (lung or peritoneal) metastases were documented in 13 patients. Metastatic disease was limited to the liver in the remaining 11 patients, with hepatic replacement less than 25 per cent in one, 25–50 per cent in four and more than 50 per cent in six patients. Small bowel diameter was 2·0 (1·7–2·2) cm and caecal diameter was 4·8 (4·2–5·0) cm. There were no intestinal fluid levels.

Clinical outcome

Colonic obstruction

Three patients with sigmoid colon tumours developed progressive incomplete colonic obstruction. The first was a

51-year-old man who presented with altered bowel habit and more than 50 per cent liver metastases. He underwent a sigmoid colectomy at 3 months following diagnosis and subsequently died from progressive disease at 19 months. The second patient was a 56-year-old woman who presented with altered bowel habit and 25–50 per cent liver metastases. She underwent endocolonic stenting at 12 months and died from progressive disease at 23 months. The third patient was a 69-year-old man who presented with dysuria and 25–50 per cent liver metastases, underwent endocolonic stenting at 20 months and is alive at 24 months. Following intervention there was no morbidity or death, good symptomatic responses were achieved and all patients continued with chemotherapy.

In addition, a 79-year-old woman, who presented with weight loss, acutely developed complete colonic obstruction 2 weeks after diagnosis. She had a sigmoid colon cancer with more than 50 per cent liver metastases and lung metastases. Stenting was technically unsuccessful and a sigmoid colostomy was performed. Postoperative deterioration in performance status precluded systemic chemotherapy and the patient died after 3 months. There was no association between the dimensions of the primary tumour or diameters of the small bowel or caecum and subsequent obstruction.

Abdominal pain

Three patients with a right colonic tumour had increasing abdominal pain but no clinical or radiological evidence of bowel obstruction. Following lack of response to medical therapy all three patients opted for right hemicolectomy. The first patient was a 71-year-old man with 25–50 per cent liver metastases and lung metastases who had presented with abdominal pain. He was operated on 2 months after diagnosis; a postoperative decline in performance status precluded chemotherapy and he died from progressive disease at 6 months. The second patient was a 66-year-old man with 25–50 per cent liver metastases who presented with weight loss, underwent operation after 5 months and died from progressive disease at 14 months. The third patient was a 71-year-old man with 25–50 per cent liver metastases who presented with weight loss, underwent operation at 11 months and is alive at 13 months. There was no operative death but the symptomatic response was uniformly poor in all three patients.

Local complications of rectal cancer

One patient with rectal cancer developed substantial tenesmus and discharge after 18 months with minimal symptoms. She had rapidly progressive liver disease and declined pelvic radiotherapy. Partial resection of the tumour by a transanal approach provided some relief of symptoms.

Potentially curative operation following downstaging by chemotherapy

A young man with a primary rectal cancer and more than 50 per cent liver metastases had a sustained partial response to oxaliplatin-containing chemotherapy. Following extensive restaging investigations, potentially curative anterior resection and right trisegmentectomy were performed synchronously 18 months after diagnosis, and the patient is alive at 24 months.

Survival characteristics

To date, 18 patients have died from clinically progressive systemic disease and another died because of a strangulated femoral hernia. Five patients are currently alive at a median follow-up of 18 (6–25) months. For the entire cohort of 24 patients, the median survival time was 10·3 (6–18) months and the actuarial survival rate was 44 per cent at 1 year (*Fig. 1*). On stratifying patients according to extent of disease, a significant association was observed between metastatic burden and survival ($P = 0{\cdot}002$, log rank test for trend).

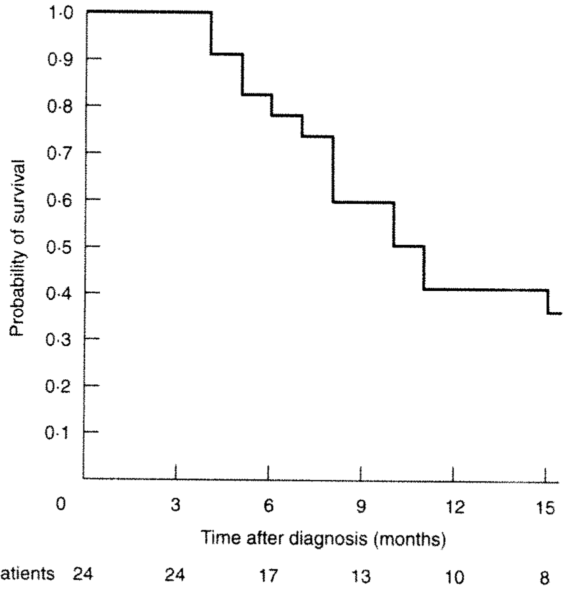


Fig. 1 Actuarial survival plot for patients with stage IV colorectal cancer who had non-operative management of the primary tumour

Discussion

Management of the patient with incurable stage IV colorectal cancer and a minimally symptomatic primary tumour poses a clinical dilemma. Of 24 such patients in whom the primary tumour was left *in situ*, three suffered progressive incomplete obstruction and one developed complete colonic obstruction. In a similar series emergency operations were required for obstruction in two of 23 patients[12]. Such a low incidence of obstruction is not unexpected as only 16 per cent of patients with colorectal cancer present with this complication[13]. Moreover, the risk of obstruction does not appear to be any higher for stage IV disease than for earlier disease stages[14]. However, the mortality rate associated with emergency surgery in patients with stage IV disease is high (27 per cent)[14]. This might be used to justify 'prophylactic' operations when the patient is asymptomatic. Such prophylactic surgery also carries substantial mortality (8 per cent)[8] and morbidity (23 per cent)[5] rates. In contrast, the authors' policy of initial non-operative management was associated with no deaths and minimum morbidity. Chemotherapy did not comprise intensely myeloproliferative schedules and, in the authors' experience of surgery during chemotherapy in general, operation during such treatment is not associated with increased morbidity. Close clinical monitoring resulting in early recognition and intervention for obstruction contributed to the favourable outcome. Obstruction was associated exclusively with tumours in the sigmoid colon. Such site specificity, which has been noted previously[12], was critical for successful deployment of endocolonic stents, which decompress the colon safely and effectively in most cases[15] and appear to be more cost effective than surgery for palliation of malignant large bowel obstruction[16]. Furthermore, the high incidence of obstruction in those with sigmoid colon cancers (four of eight patients) implies a potential role for selective early intervention in situations in which close monitoring might not be possible. Prophylactic intervention has previously been recommended selectively for patients with a low metastatic burden who are presumed to be at high risk of obstruction because of their relatively long survival[5–7]. Both the present study and that of Scoggins *et al.*[12] confirm the survival advantage of patients with a low metastatic burden but do not show any association between the incidence of complications and extent of metastatic disease.

Three patients underwent right hemicolectomy for abdominal pain of unclear aetiology, with poor symptomatic relief. For patients with advanced cancer, pain is often multifactorial and includes somatic, visceral, neuropathic, sympathetically mediated and psychological dimensions. For example, intestinal colic may be due to disordered bowel motility, caused by tumour infiltration of the coeliac and mesenteric plexuses, or diffuse extramural bowel obstruction by omental masses or malignant adhesions and, consequently, symptom control by surgery may be limited[17]. Optimal pharmacological therapy[18] or external-beam radiation for hepatic capsular pain[2] are valuable modalities but it is frequently difficult to withhold an operation in the face of continuing abdominal symptoms.

Only one patient with rectal cancer suffered problematic tenesmus and discharge. Although previous authors have recommended resection of the rectum to prevent such problems[19], several low-risk therapeutic alternatives are now available, such as external-beam or endocavitary radiation[20], neodymium yttrium–aluminium–garnet laser therapy[21], cryosurgery[22] or transanal debulking of the tumour[23].

One patient underwent potentially curative rectal and hepatic resection following chemotherapy. This strategy emphasizes the need to evaluate the response to chemotherapy and subsequently reconsider a potentially curative operation, which may yield encouraging results for carefully selected patients[24].

The overall median survival interval was 10·3 months. A similar median survival period (10·2 months) has been reported recently in another series of patients with incurable stage IV disease, who received systemic chemotherapy[5]. The majority of these patients, however, had resection of the primary tumour with substantial associated morbidity (23 per cent) and mortality (6 per cent) rates. Comparison with the present series suggests that resection of the primary tumour does not confer any long-term survival advantage. This observation is supported by Scoggins *et al.*[12], who reported similar survival characteristics for their group of non-operatively managed patients and a matched group that underwent resection of the primary tumour.

In conclusion, administration of systemic chemotherapy and symptom-directed intervention for the primary tumour is a safe and effective approach. Detailed patient counselling, close clinical monitoring and efficient liaison between medical and surgical oncologists is essential. A multicentre clinical trial that randomizes patients with sigmoid colon tumours to either early operation or symptom-directed intervention only, and includes measurement of quality of life and chemotherapy-related morbidity, is needed.

Acknowledgements

The authors are grateful to the following clinicians who were involved in the management of patients included in the study: Mr N. S. Ambrose, Mr M. R. Lansdown and Dr P. Patel (St James's University Hospital, Leeds), Mr P. Finan, Mr H. Sue-Ling and Professor D. Johnson (General Infirmary at Leeds), and Professor J. Cassidy (Grampian University Hospital, Aberdeen). This work was supported financially by Yorkshire Cancer Research, the Medical Research Council and the Imperial Cancer Research Fund.

References

1 Cancer Research Campaign. *CancerStats: Large Bowel – UK Report*. London: Cancer Research Campaign, 2000.

2 Millikan KW, Staren ED, Doolas A. Invasive therapy of metastatic colorectal cancer to the liver. *Surg Clin North Am* 1997; **77:** 27–48.

3 Bacon HE, Martin PV. The rationale of palliative resection for primary cancer of the colon and rectum complicated by liver and lung metastasis. *Dis Colon Rectum* 1964; **7:** 211–17.

4 Oxley EM, Ellis H. Prognosis of carcinoma of the large bowel in the presence of liver metastases. *Br J Surg* 1969; **56:** 149–52.

5 Rosen SA, Buell JF, Yoshida A, Kazsuba S, Hurst R, Michelassi F *et al.* Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg* 2000; **135:** 530–5.

6 Joffe J, Gordon PH. Palliative resection for colorectal carcinoma. *Dis Colon Rectum* 1981; **24:** 355–60.

7 Liu SKM, Church JM, Lavery IC, Fazio VW. Operation in patients with incurable colon cancer – is it worthwhile? *Dis Colon Rectum* 1997; **40:** 11–14.

8 Mella J, Biffin A, Radcliffe AG, Stamatakis JD, Steele RJC. Population-based audit of colorectal cancer management in two UK health regions. Colorectal Cancer Working Group, Royal College of Surgeons of England Clinical Epidemiology and Audit Unit. *Br J Surg* 1997; **84:** 1731–6.

9 Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *BMJ* 2000; **321:** 531–5.

10 Sarela A, O'Riordain DS. Rectal adenocarcinoma with liver metastases: management of the primary tumour. *Br J Surg* 2001; **88:** 163–4.

11 de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997; **15:** 808–15.

12 Scoggins CR, Meszoely IM, Blanke CD, Beauchamp RD, Leach SD. Nonoperative management of primary colorectal cancer in patients with stage IV disease. *Ann Surg Oncol* 1999; **6:** 651–7.

13 Serpell JW, McDermott FT, Katrivessis H, Hughes ESR. Obstructing carcinomas of the colon. *Br J Surg* 1989; **76:** 965–9.

14 Stamatakis J, Thompson M, Chave H, Kinsman R. National audit of bowel obstruction due to colorectal cancer April 1998–March 1999. *The Association of Coloproctology of Great Britain and Ireland*, London. 2000.

15 Camunez F, Echenagusia A, Simo G, Turegano F, Vazquez J, Barreiro-Meiro I. Malignant colorectal obstruction treated by means of self-expanding metallic stents: effectiveness before surgery and in palliation. *Radiology* 2000; **216:** 492–7.

16 Cole SJ, Boorman P, Osman H, Sathananthan N, Parker MC. Endoluminal stenting for relief of colonic obstruction is safe and effective. *Colorectal Dis* 2000; **2:** 282–7.

17 Feuer DJ, Broadley KE, Shepherd JH, Barton DP. Systematic review of surgery in malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. The Systematic Review Steering Committee. *Gynecol Oncol* 1999; **75:** 313–22.

18 Hardy JR. Medical management of bowel obstruction. *Br J Surg* 2000; **87:** 1281–3.

19 Moran MR, Rothenberger DA, Lahr CJ, Buls JG, Goldberg SM. Palliation for rectal cancer. Resection? Anastomosis? *Arch Surg* 1987; **122:** 640–3.

20 Farouk R, Nelson H, Gunderson LL. Aggressive multimodality treatment for locally advanced irresectable rectal cancer. *Br J Surg* 1997; **84:** 741–9.

21 Farouk R, Ratnaval CD, Monson JR, Lee PW. Staged delivery of Nd : YAG laser therapy for palliation of advanced rectal carcinoma. *Dis Colon Rectum* 1997; **40:** 156–60.

22 Meijer S, Rahusen FD, van der Plas LG. Palliative cryosurgery for rectal carcinoma. *Int J Colorectal Dis* 1999; **14:** 177–80.

23 Turler A, Schafer H, Pichlmaier H. Role of transanal endoscopic microsurgery in the palliative treatment of rectal cancer. *Scand J Gastroenterol* 1997; **32:** 58–61.

24 Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D *et al.* Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; **224:** 509–22.

Prevention of the neoplastic progression of Barrett's oesophagus by endoscopic argon beam plasma ablation

C. D. Morris, J. P. Byrne, G. R. A. Armstrong and S. E. A. Attwood

Department of Upper Gastrointestinal Surgery, Hope Hospital, Stott Lane, Salford, Manchester M6 8HD, UK
Correspondence to: Mr S. E. A. Attwood (e-mail: sattwood@hope.srht.nwest.nhs.uk)

Background: Patients with Barrett's oesophagus have a risk of approximately 1 per 100 patient-years for the development of oesophageal adenocarcinoma. Endoscopic ablation of Barrett's oesophagus has been shown to lead to the regrowth of a 'neo' squamous epithelium if gastro-oesophageal reflux is controlled, but the incidence of subsequent tumour formation is unknown.

Methods: The follow-up of 55 patients who underwent endoscopic ablation of Barrett's oesophagus by argon beam plasma coagulation (ABPC) is reported. Of the 55 patients, nine had low-grade dysplasia, nine had high-grade dysplasia and the remainder had non-dysplastic Barrett's metaplasia. Twelve patients had reflux control by antireflux surgery and the remainder received proton pump inhibitor therapy. Barrett's metaplasia was ablated by ABPC to within 2 cm of the gastro-oesophageal junction.

Results: To date, one patient has died and one patient was unable to complete treatment. The remaining patients were followed by regular endoscopic surveillance for a mean of 38·5 months to give a total follow-up of 173·5 patient-years. No malignancy has developed in any patient during follow-up.

Conclusion: The absence of malignant complications in this study of prophylactic ablation of long-segment Barrett's oesophagus strengthens the argument for endoscopic ablation in the prevention of oesophageal adenocarcinoma.

Paper accepted 24 July 2001

British Journal of Surgery 2001, **88**, 1357–1362

Introduction

Three decades ago oesophageal adenocarcinoma was considered a rare malignancy. A review of 1312 cases of oesophageal carcinoma at the Mayo Clinic from 1946 to 1963 showed that adenocarcinoma accounted for only 0·76 per cent of all tumours[1]. Over the past 30 years, however, Western populations have witnessed a dramatic change, with the incidence of adenocarcinoma rising by 10 per cent annually, while the incidence of squamous carcinoma remains unchanged[2]. Taken together with adenocarcinomas of the gastric cardia and gastro-oesophageal junction, which seem to be part of the same disease entity, it now represents the fastest growing cancer in the Western world[2,3]. Most recent data from the North-West of England and Wales regions confirm the rising incidence, with oesophageal carcinoma occurring in 12–14 per 100 000 males[4,5], and adenocarcinomas outnumbering squamous cell carcinomas[6]. This is likely to be an underestimate of the current incidence.

The strongest risk factor for the development of oesophageal adenocarcinoma is Barrett's oesophagus, a columnar metaplasia of the lower oesophageal epithelium, which occurs in approximately 10 per cent of patients with gastro-oesophageal reflux disease (GORD)[7]. These patients have a 1 per cent annual risk of developing adenocarcinoma[8–10], 30–125 times the risk seen in the general population[11]. Despite advances in the management of the disease, the prognosis remains depressing, with a crude 3-year survival rate of around 8 per cent and median survival of 5 months overall[4]. In patients with resectable disease the 5-year survival rate is around 20 per cent, with a median survival of 18 months[5,12].

Because of the poor prognosis of these tumours once established, much attention has focused on the prevention of neoplastic progression in Barrett's oesophagus. One possible mechanism that has received much attention recently is ablation of the Barrett's metaplasia. Control of GORD alone by medical[13] or surgical[14] methods appears to have only a minimal effect in reducing the extent of Barrett's metaplasia despite up to 24 months of medical treatment[13]. The adaptation of endoscopic techniques such as KTP/Nd-YAG laser[15], multipolar electrocoagulation[16], photodynamic therapy[17] and argon beam plasma coagulation

(ABPC)[18], conventionally used for the palliation of malignant tumours within the gastrointestinal tract, has led to successful ablation of Barrett's oesophagus. Without control of gastro-oesophageal reflux the columnar mucosa regrows. However, if adequate reflux control is achieved, by either medical or surgical means, the denuded area is re-epithelialized by squamous epithelium[18].

In this unit, initial experience with the use of ABPC for Barrett's ablation in 30 patients was reported in 1998[18]. This technique involves the application of a high-frequency current carried to the tissue via a flow of ionized argon gas. It is a non-contact technique and the current is able to travel a few millimetres to the nearest point of electrical contact carried within the gas flow. As an area becomes burnt and dried, its electrical conductivity decreases resulting in no further energy flow to that area and limiting the depth of injury. The depth of injury required to eradicate the epithelium has been estimated to be 0·6 mm from pathological studies[19] and the depth of penetration obtained with ABPC therefore provides adequate tissue destruction[20] with low risk of perforation or stricture formation due to deeper muscularis propria damage[20,21].

The neoplastic potential of this new squamous epithelium is unknown. To date, all studies examining ablation techniques with the goal of preventing neoplastic progression of benign Barrett's metaplasia have involved a small number of patients or short periods of follow-up, and have concentrated primarily on the feasibility of ablating the Barrett's metaplasia with the subsequent regrowth of a squamous lining. Now this has been established, attention must be focused on whether the ablation of Barrett's metaplasia can safely reduce the incidence of malignant progression.

Patients and methods

Patients

Fifty-five patients with long segment (more than 3 cm) Barrett's oesophagus underwent ablation. Patients with low-grade dysplasia (LGD) and high-grade dysplasia (HGD) were also included. All patients with dysplasia underwent thorough endoscopic biopsy before ablation to exclude invasive adenocarcinoma and diagnoses of HGD were confirmed by a second pathologist. All patients had control of gastro-oesophageal reflux by either proton pump inhibitor (PPI) therapy or antireflux surgery before ablation, with the PPI dose titrated to provide abolition of reflux symptoms. Twenty-four-hour pH monitoring on treatment was carried out only in patients who failed to show satisfactory symptom control. The study was approved by the local research ethics committee and informed consent was obtained from all patients.

Ablation technique

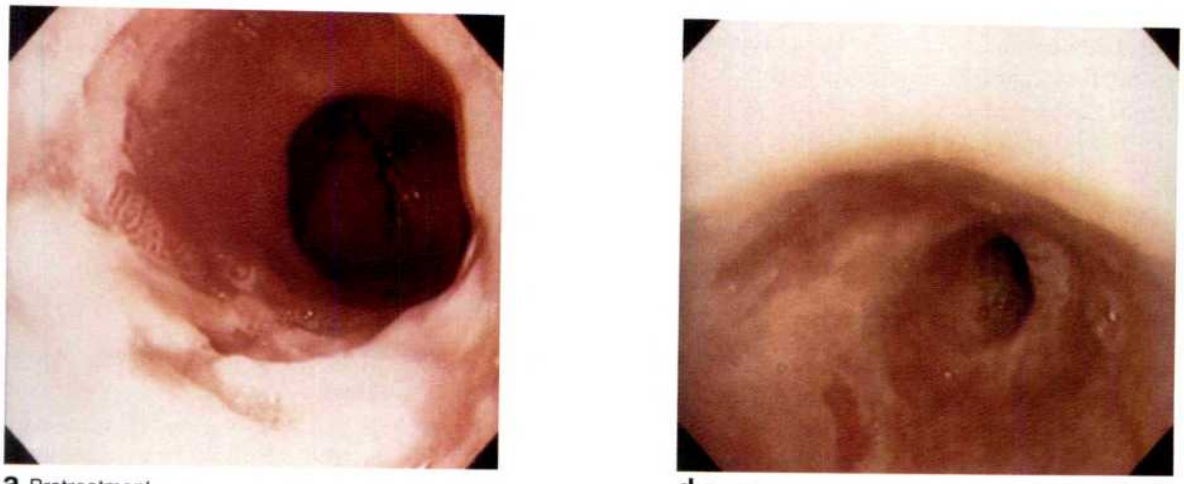
All ABPC treatments were carried out as a day-case procedure under intravenous sedation with midazolam 5–10 mg. Non-invasive monitoring of pulse, blood pressure and pulse oximetry were carried out routinely. Ablation was performed using the ERBE 'Beamer 2' electrosurgery unit (ERBE Elektromedezin, Tubingen, Germany) via a double-channel therapeutic gastroscope. Following oesophageal intubation the ABPC probe was protruded from the end of the endoscope by 1 cm and positioned 1–2 mm from the epithelium to be ablated. A longitudinal strip was ablated by gradually withdrawing the scope to the upper extent of the Barrett's metaplasia. The gastroscope was then advanced after withdrawing the tip of the ABPC probe to prevent inadvertent perforation. The procedure was then repeated on adjacent mucosa until a strip of epithelium 1–2 cm wide was ablated. Early in the series the full length of a long Barrett's segment was not ablated in one session, and ablation was carried out in segments 3–5 cm long.

The columnar metaplasia (*Fig. 1a*) was ablated in three longitudinal columns with intervening mucosal bridges left intact (*Fig. 1b*). At a further session 4 weeks later (*Fig. 1c*), the intervening bridges were ablated. Any residual areas of metaplasia (*Fig. 1d*) were ablated at the time of follow-up endoscopy (*Fig. 1e*) until the oesophagus was lined by squamous epithelium (*Fig. 1f*). Ablation of the entire Barrett's segment to within 1 cm of the gastro-oesophageal junction was attempted in all patients. During the ablation, the insufflated argon gas was aspirated at regular intervals to prevent excessive gastric distension. Patients were kept 'nil by mouth' until full recovery from sedation and oral analgesia was provided as required.

Correlation between the reduction in Barrett's length and the number of treatment sessions was sought by calculating the Pearson's correlation coefficient (Microsoft Excel 2000®; Microsoft Corporation, Redmond, Washington, USA) and a *P* value obtained using 50 degrees of freedom.

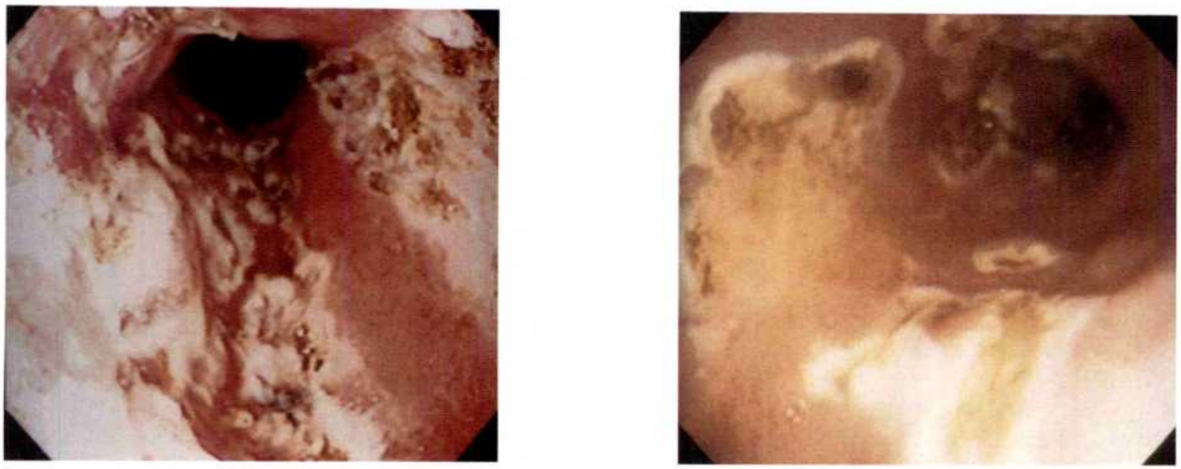
Follow-up data collection

Following successful ablation patients were routinely followed clinically and endoscopically at 6-month intervals for 12 months, then at yearly intervals. Patients with HGD were initially reviewed at 3-month intervals for 6 months. At endoscopy, random biopsies were taken at 1-cm intervals throughout the full extent of the neosquamous epithelium along with targeted biopsies of any irregular areas. Biopsies



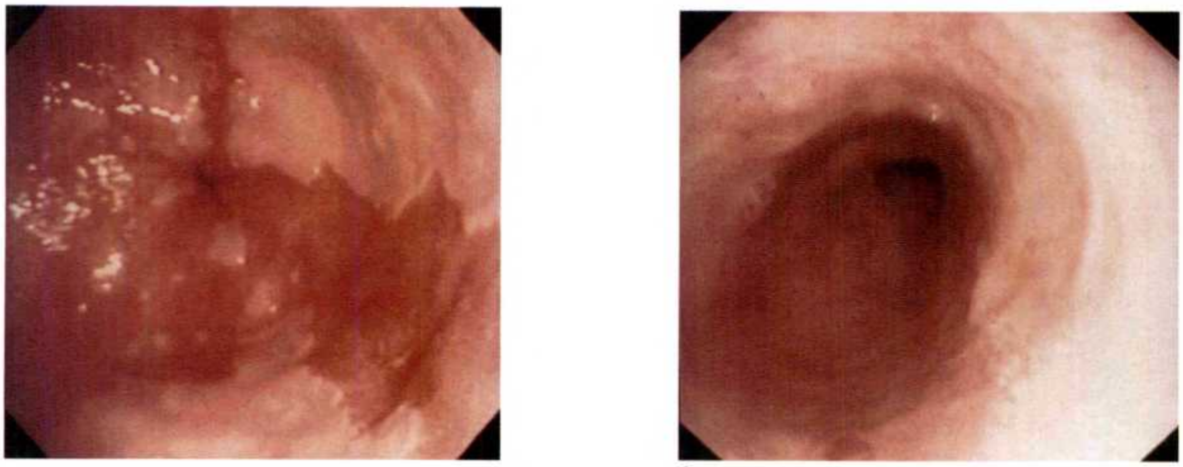
a Pretreatment

d Residual islands of metaplasia



b Initial ablation

e Residual islands ablated



c 4 weeks post-ablation

f Final appearance

Fig. 1 Endoscopic views of the ablation sequence. **a** Pretreatment Barrett's oesophagus; **b** initial ablation in three longitudinal strips; **c** appearance 4 weeks after initial ablation; **d** residual islands of metaplasia; **e** ablation of residual metaplastic islands; and **f** final appearance of neosquamous lined oesophagus (note single residual metaplastic island; this was subsequently ablated)

were stained with haematoxylin and eosin, and examined for any degree of histological atypia or the presence of residual 'buried' intestinal metaplasia.

Results

Fifty-five patients underwent ABPC ablation. Nine patients had HGD, nine had LGD and the remainder had benign metaplasia only. Twelve patients had reflux control by antireflux surgery before inclusion, and the remaining patients were maintained on proton pump inhibitor therapy. All patients on PPI therapy had the dose titrated to provide symptom relief (omeprazole 20–60 mg). Two patients did not complete the ablation therapy; the remaining 53 patients have been followed for a mean(s.d.) of 38·5(14·6) months to give a total follow-up of 173·5 patient-years. The mean follow-up in those with any degree of dysplasia or HGD alone was 31·3(17·7) and 20·8(18·4) months respectively. No adenocarcinomas developed in any patient following ablation. No patient with initial benign metaplasia progressed to any degree of dysplasia. All patients with initial dysplasia who completed the ablation therapy had regression of the dysplasia with no subsequent recurrence.

The mean(s.d.) length of Barrett's epithelium before ablation was 6·06(3·15) cm. Barrett's epithelium was ablated to within 1 cm of the gastro-oesophageal junction in all but four patients. Two patients were unable to complete ablation and are discussed further below. The other two patients had 17 and 12 cm of metaplasia initially. After seven and six treatment sessions, respectively, neosquamous epithelium extended to within 2 cm of the gastro-oesophageal junction and ablation was considered successful. The mean(s.d.) reduction in Barrett's segment length was 5·00(2·37) cm in those completing ablation. The mean(s.d.) number of treatment sessions was 3·02(1·69) and there was a significant correlation between the reduction in Barrett's length and the number of treatment sessions (Pearson's coefficient 0·60, $P < 0.01$). Sixteen (30 per cent) of the 53 patients have had areas of intestinal metaplasia detected beneath the neosquamous epithelium on routine histological examination of biopsies taken from the ablated epithelium.

Two patients suffered oesophageal perforation. Both patients developed chest pain and mediastinal emphysema associated with a tachycardia immediately after ABPC treatment. The first patient underwent drainage via a thoracotomy but died from respiratory failure shortly afterwards. The second patient was kept nil-by-mouth for 5 days and treated with total parenteral nutrition. He made an uneventful recovery and has subsequently shown regrowth of squamous mucosa to within 1 cm of the gastro-oesophageal junction. One further patient required readmission to hospital with chest pain following the initial treatment. There was no evidence of perforation and the symptoms settled within 3 days. At the next treatment session, the procedure had to be abandoned owing to recurrence of pain and no further treatments were attempted. No other complications were encountered.

Discussion

Previous studies detailing ablation of Barrett's oesophagus have described the feasibility and efficacy of the techniques, and have provided no data to support a reduction in malignant risk. The risk of adenocarcinoma development in Barrett's oesophagus is approximately 1 per 100 patient-years of follow-up and current literature suggests that around 50 per cent of patients with unifocal HGD will progress to invasive adenocarcinoma or multifocal HGD within 3 years[22]. Indeed, up to 50 per cent of patients with HGD may have microscopic evidence of invasive adenocarcinoma at diagnosis if examined closely[23,24] and not all malignancies will be detected even after repeat endoscopy and thorough biopsy[23]. Approximately five or six patients within this cohort, which includes nine patients with HGD, would therefore have been expected to undergo malignant progression during the follow-up period of 173·5 patient-years. The lack of any malignancy within this group is therefore encouraging. Unfortunately a case-controlled comparison within this surveillance programme would not be possible as all patients who develop HGD undergo surgical resection or ABPC ablation of the dysplastic areas.

Two oesophageal perforations occurred early in the study. The first patient had HGD but was unfit for surgical resection owing to significant cardiorespiratory co-morbidity. On recognition of the perforation and following frank discussion regarding the risks of surgery, the patient decided to undergo drainage via a thoracotomy but died after operation from respiratory failure. The second patient was treated successfully by conservative means. Following these complications there have been no further perforations in the subsequent 300 ABPC treatments, and the authors believe that the two observed were associated with the early learning curve. They are likely to be caused by perforation of the wall by an ABPC probe protruding from the endoscope during coughing or advancement of the endoscope, or by accidental repeated coagulation of the same area.

Although this study suggests a significant potential role for ABPC, questions remain regarding the long-term neoplastic potential of the new squamous epithelium. Residual malignant potential could be derived from two areas: the neosquamous epithelium itself or residual intestinal metaplasia buried beneath it. These buried glands are formed when superficial destruction of the surface mucosa leaves deeper glandular areas undamaged. The re-epithelialization of the surface then leads to the glands being buried. There are no clear data on whether this residual metaplasia maintains a malignant potential, or whether the combination of reflux control and protection from noxious agents by the covering squamous epithelium halts any potential progression. There are two case reports of oesophageal adenocarcinoma development following Barrett's ablation[25,26]. Both apparently developed underneath the new squamous epithelium, raising the possibility that they may have arisen from intestinal metaplasia buried beneath. Although there was no evidence of malignancy before ablation in either case, the development of invasive malignancy within 18 and 6 months of ablation may suggest the presence of foci of dysplasia missed before ablation. It is presumed that any technique that reduces the number of potentially malignant cells, in conjunction with reflux control to prevent further noxious injury, is likely to result in a substantially lower risk of malignant progression.

In summary, this study demonstrates that ABPC is an effective, inexpensive method of Barrett's ablation. The lack of any malignancy during follow-up, including patients with initial HGD, suggests it may be an effective method for the prevention of oesophageal adenocarcinoma. Further studies are under way to characterize the neosquamous epithelium and the buried intestinal metaplasia beneath it. The data presented would justify a formal randomized controlled trial of ABPC in the prevention of adenocarcinoma in Barrett's oesophagus.

Acknowledgements

C.D.M. is supported by a research fellowship from the Royal College of Surgeons of England. The authors thank the Astra Foundation UK for the purchase of the ERBE argon beam plasma coagulator.

References

1 Raphael H, Ellis F, Docherty M. Primary adenocarcinoma of the oesophagus: 18 year review and review of the literature. *Ann Surg* 1966; **164:** 785–96.

2 Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265:** 1287–9.

3 Blot WJ, Devesa SS, Fraumeni JF Jr. Continuing climb in rates of esophageal adenocarcinoma. an update. *JAMA* 1993, **270:** 1320.

4 Byrne J. Adenocarcinoma of the lower oesophagus and oesophagogastric junction: epidemiology, aetiology and factors which may reduce cancer risk. *MD Thesis*, University of Manchester, Manchester, 1997.

5 Pye JK, Crumplin MK, Charles J, Kerwat R, Foster ME, Biffin A. One-year survey of carcinoma of the oesophagus and stomach in Wales. *Br J Surg* 2001; **88:** 278–85.

6 Byrne JP, Parry JM, Woodman CJB, Attwood SEA. The epidemiology of adenocarcinoma of the oesophagus and gastric cardia in the North West of England. In: Giuli R, Galm JP, Jamieson GG, Scarpignato C, eds. *O.E.S.O. The Esophagogastric Junction.* Paris: John Libbey Eurotext, 1998: 1140–4.

7 Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium Gastroenterology Outcomes Research Group in Endoscopy. *Am J Gastroenterol* 1997, **92:** 1293–7.

8 Williamson WA, Ellis FH Jr, Gibb SP, Shahian DM, Aretz HT, Heatley GJ *et al.* Barrett's esophagus. Prevalence and incidence of adenocarcinoma. *Arch Intern Med* 1991; **151:** 2212–16.

9 Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology* 1989; **96:** 1249–56.

10 Spechler SJ, Robbins AH, Rubins HB, Vincent ME, Heeren T, Doos WG *et al.* Adenocarcinoma and Barrett's esophagus. An overrated risk? *Gastroenterology* 1984, **87:** 927–33.

11 Reed P. Changing pattern of oesophageal cancer. *Lancet* 1991; **338:** 178.

12 Thomas P, Doddoli C, Lienne P, Morati N, Thirion X, Garbe L *et al.* Changing patterns and surgical results in adenocarcinoma of the oesophagus. *Br J Surg* 1997; **84:** 119–25.

13 Peters FT, Ganesh S, Kuipers EJ, Sluiter WJ, Klinkenberg-Knol EC, Lamers CB *et al.* Endoscopic regression of Barrett's oesophagus during omeprazole treatment, a randomised double blind study. *Gut* 1999; **45:** 489–94.

14 Attwood SE, Barlow AP, Norris TL, Watson A. Barrett's oesophagus. effect of antireflux surgery on symptom control and development of complications. *Br J Surg* 1992; **79:** 1050–3.

15 Sampliner RE, Hixson LJ, Fennerty MB, Garewal HS. Regression of Barrett's esophagus by laser ablation in an anacid environment. *Dig Dis Sci* 1993; **38:** 365–8.

16 Sampliner RE, Fennerty B, Garewal HS. Reversal of Barrett's esophagus with acid suppression and multipolar electrocoagulation: preliminary results. *Gastrointest Endosc* 1996; **44:** 532–5.

17 Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. *Gastrointest Endosc* 1999; **49:** 1–7.

18 Byrne JP, Armstrong GR, Attwood SE. Restoration of the normal squamous lining in Barrett's esophagus by argon beam plasma coagulation. *Am J Gastroenterol* 1998; **93:** 1810–15.

19 Ackroyd R, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Ablation treatment for Barrett's oesophagus: what depth of tissue destruction is needed? *J Clin Pathol* 1999; **52:** 509–12.

20 Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation. First clinical experiences in flexible endoscopy. *Endosc Surg Allied Technol* 1994; **2:** 42–6.

21 Watson JP, Bennett MK, Griffin SM, Matthewson K. The tissue effect of argon plasma coagulation on esophageal and gastric mucosa. *Gastrointest Endosc* 2000; **52:** 342–5.
22 Weston AP, Sharma P, Topalovski M, Richards R, Cherian R, Dixon A. Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000; **95:** 1888–93.
23 Zaninotto G, Parenti AR, Ruol A, Costantini M, Merigliano S, Ancona E. Oesophageal resection for high-grade dysplasia in Barrett's oesophagus. *Br J Surg* 2000; **87:** 1102–5.
24 Altorki NK, Sunagawa M, Little AG, Skinner DB. High-grade dysplasia in the columnar-lined esophagus. *Am J Surg* 1991; **161:** 97–9.
25 Van Laethem JL, Peny MO, Salmon I, Cremer M, Deviere J. Intramucosal adenocarcinoma arising under squamous re-epithelialisation of Barrett's oesophagus. *Gut* 2000; **46:** 574–7.
26 Bonavina L, Ceriani C, Carazzone A, Segalin A, Ferrero S, Peracchia A. Endoscopic laser ablation of nondysplastic Barrett's epithelium: is it worthwhile? *J Gastrointest Surg* 1999; **3:** 194–9.

Association of Surgeons

Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery

G. Sanders, S. J. Mercer, K. Saeb-Parsey, M. A. Akhavani, K. B. Hosie and A. W. Lambert

Colorectal Unit, Department of Surgery, Derriford Hospital, Plymouth PL6 8DH, UK
Correspondence to Mr A. W. Lambert (e-mail anthony.lambert@phnt.swest.nhs.uk)

Background: Bowel preparation using purgatives has previously been shown significantly to increase haemoglobin concentration and decrease weight. This prospective randomized study assessed the effects of administering intravenous fluid during bowel preparation.

Methods: Patients having bowel preparation with Picolax® for colonic procedures were randomized prospectively to receive no intravenous fluid (group 1) or calculated intravenous crystalloid based on body-weight (group 2) during preparation. Physiological, haematological and biochemical variables were measured before and after bowel preparation.

Results: Forty-one patients were recruited with a median age of 69 (range 29–86) years, 22 in group 1 and 19 in group 2. There was no difference between groups in any of the variables measured before bowel preparation. On completion, there was a significant difference between groups in mean weight loss ($P = 0{\cdot}01$), postural change in systolic pressure ($P = 0{\cdot}015$) and serum creatinine concentration ($P = 0{\cdot}008$). In addition there was a significant fall in erect blood pressure after bowel preparation in group 1 ($P = 0{\cdot}02$). The mean urine output in group 1 was 982 ml and in group 2 was 1808 ml ($P = 0{\cdot}004$). The faeces weight between groups was not significantly different.

Conclusion: Picolax® bowel preparation has a significant dehydrating effect, which can be minimized by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study).

Paper accepted 1 June 2001

British Journal of Surgery 2001, 88, 1363–1365

Introduction

Two sachets of Picolax® (Ferring Pharmaceuticals, Langley, UK) are administered to patients for bowel preparation before colonic surgery in our unit. Sodium picosulphate is hydrolysed in the colon to reduce water and electrolyte absorption, while magnesium citrate acts as an osmotic laxative. It was our impression that a large number of patients receiving bowel preparation were dehydrated when they came to surgery. This prospective randomized controlled study assessed the effects of administering intravenous fluid during bowel preparation.

Patients and methods

Patients receiving bowel preparation for colonic procedures were recruited. Patients in group 1 were randomized by sealed envelope to receive no intravenous fluid while those in group 2 received a calculated volume of intravenous normal saline during bowel preparation, starting at the same time as Picolax® administration (intravenous infusion rate per h 4 ml per kg for the first 10 kg, 2 ml per kg for the second 10 kg then 1 ml per kg for each subsequent kilogram)[1]. Both groups received two sachets of Picolax® 6 h apart, starting 18 h before operation, and were encouraged to drink unlimited clear fluids until 6 h before that time. The study received approval from the Plymouth local research ethics committee and patients were required to give informed consent for inclusion.

Physiological (weight, pulse, supine and erect blood pressure), haematological (haemoglobin, haematocrit) and biochemical (sodium, potassium, urea, creatinine, urine osmolality) variables were measured immediately before starting bowel preparation and repeated 1 h before procedure or immediately before premedication. Weight was measured to the nearest 0·5 kg using a single Seca (Hamburg, Germany) analogue scale, which was checked annually by the Bristol Scales Company (Bristol, UK). Care was taken to ensure that the same clothing was worn at both weighings. Blood pressure and heart rate were measured with a Dinamap Compact TS (Johnson and Johnson Medical, Tampa, Florida, USA). Supine readings were taken after lying undisturbed for 30 min. Subsequent erect readings were taken 2 min after sitting or standing. In addition, total fluid intake and output, American Society of Anesthesiologists (ASA) grade[2], and weight of faeces were recorded. Fluid intake included oral and intravenous fluids.

A sample size of 20 in each group was calculated, based on finding a difference in weight between groups of 0·5 kg with a standard deviation of 0·55[3], power of 80 per cent and significance level of 0·05. Data were assessed for normality using the Shapiro Wilk test and subsequently analysed within groups and between groups using paired and unpaired t tests as appropriate. $P < 0{\cdot}05$ was taken as significant.

Results

Forty-one patients were recruited with a median age of 69 (range 29–86) years; there were 22 in group 1 and 19 in group 2. There were 26 men and 15 women. There was no difference between groups in baseline variables, age, sex, ASA grade or diagnosis before bowel preparation, and no evidence of non-normality in any of the variables studied. On completion (*Tables 1* and *2*), there was a significant difference between groups in mean weight loss ($P = 0{\cdot}01$), postural change in systolic pressure ($P = 0{\cdot}015$) and serum creatinine level ($P = 0{\cdot}008$). In addition there was a significant change in weight within group 1 ($P < 0{\cdot}001$), fall in erect systolic pressure ($P = 0{\cdot}011$), fall in erect diastolic pressure ($P = 0{\cdot}023$) and fall in supine diastolic pressure ($P = 0{\cdot}005$). Serum potassium concentration decreased significantly in groups 1 and 2 ($P = 0{\cdot}019$ and $P < 0{\cdot}001$ respectively) and supine pulse rate increased significantly in both groups ($P = 0{\cdot}046$ and $P = 0{\cdot}047$ respectively). The mean difference in fluid input in the two groups was 2078 ml. The mean urine output in group 1 was 982 ml and that in group 2 was 1808 ml ($P = 0{\cdot}004$) but the faeces weight was not significantly different between groups (*Table 3*).

Discussion

Picolax® bowel preparation has previously been shown to cause a significantly greater weight loss and increased

Table 1 Change in body-weight and serum creatinine level with Picolax® bowel preparation

	Group	Initial	Change
Weight (kg)	1	77·8(3·9)	− 1·6(0·2)*
	2	75·1(3·1)	− 0·5(0·3)‡
Creatinine (μmol/l)	1	96·5(6·0)	+ 1·8(1·5)
	2	91·6(4·8)	− 3·8(1·3)†§

Values are mean(s.e.m.). $^*P < 0{\cdot}001$, $^†P = 0{\cdot}009$ *versus* initial (paired t test); $^‡P = 0{\cdot}01$, $^§P = 0{\cdot}008$ *versus* group 1 (independent samples t test)

Table 3 Fluid intake *versus* urine output and faecal loss

	Group 1	Group 2	P*
Fluid intake (ml)	1669(254)	3747(359)*	< 0·001
Urine output (ml)	982(129)	1808(253)	0·004
Faecal weight (g)	1203(182)	1183(139)	n.s.

Values are mean(s.e.m.). *Mean intravenous input 2 litres, mean oral intake 1·7 litres. n.s., Not significant. *independent samples t test

Table 2 Blood pressure, pulse and serum potassium concentration before and after Picolax®

	Group	Initial	Final	P*
Postural pressure drop (mmHg)	1	− 1·6(3·4)	7·2(4·0)	n.s.
	2	− 2·9(2·9)	− 5·7(3·1)	n.s.
Erect systolic pressure (mmHg)	1	145(4)	132(6)	0·011
	2	142(4)	137(5)	n.s.
Erect diastolic pressure (mmHg)	1	84(2)	77(3)	0·023
	2	84(2)	80(4)	n.s.
Supine diastolic pressure (mmHg)	1	81(2)	75(2)	0·005
	2	79(2)	79(2)	n.s.
Potassium (mmol/l)	1	4·4(0·1)	4·1(0·1)	0·019
	2	4·4(0·1)	4·1(0·1)	< 0·001
Supine pulse (beats/min)	1	77(3)	82(2)	0·046
	2	76(3)	82(3)	0·047

Values are mean(s.e.m.). There was a significant difference in postural pressure drop between groups after Picolax® ($P = 0{\cdot}015$, independent samples t test). n.s., Not significant. *paired t test haemoglobin concentration compared with a group of matched patients undergoing body surface surgery[3]. Patients of ASA grade 3 were noted to feel faint on standing, after bowel preparation. Kutt *et al.*[4] also demonstrated an increase in haemoglobin concentration before barium enema examination. In addition there was a correlation between patients with a raised haemoglobin level and those experiencing headache. In a retrospective study, Lee *et al.*[5] examined perioperative and postoperative fluid requirements in patients undergoing inpatient *versus* outpatient bowel preparation. The inpatient group was given intravenous fluids overnight whereas the outpatient group commenced intravenous fluids 1–2 h before surgery. Although there was a shorter length of stay in the outpatient group, these patients also had increased perioperative and postoperative fluid requirements. In a prospective randomized study Lawrance *et al.*[6] studied five different oral fluid regimens in 197 patients and found no difference in any of the groups with regard to adverse events. Hill *et al.*[7] demonstrated that patients with cellular potassium depletion were at risk of hypokalaemia after bowel preparation with sodium phosphate.

The present study confirms the dehydrating effect of Picolax® bowel preparation as measured by the decrease in weight, erect systolic, erect diastolic and supine diastolic pressures in group 1, and the significant difference in postural pressure change between groups. None of these variables changed significantly in group 2, indicating that the dehydrating effect was negated with the administration of intravenous saline. Interestingly, although both groups were encouraged to drink unlimited clear fluids during preparation, their oral intake was not significantly different (*Table 3*). In both groups the serum potassium concentration decreased significantly. The supine pulse rate increased significantly in both groups, implying a cause other than hypovolaemia.

In conclusion, Picolax® bowel preparation has significant clinical effects, which may be particularly detrimental in elderly or cardiovascularly compromised patients. The dehydrating effects can be minimized by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study). Consideration should also be given to potassium replacement.

Acknowledgements

The authors thank Mr A. J. Brodribb and Mr C. Brown for allowing reporting of their patients and Dr S. Shaw, Department of Mathematics and Statistics, University of Plymouth, for advice on the statistical analysis.

References

1. Advanced Life Support Group. *Advanced Paediatric Life Support, The Practical Approach*. 2nd ed. London: BMJ Publishing Group, 1997.
2. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* 1941; **2**: 281–5.
3. Barker P, Trotter T, Hanning C. A study of the effect of Picolax on body weight, cardiovascular variables and haemoglobin concentration. *Ann R Coll Surg Engl* 1992; **74**: 318–19.
4. Kutt E, Hall MJ, Booth A, Virjee J. Barium enemas are a headache. *Clin Radiol* 1988; **39**: 9–10.
5. Lee EC, Roberts PL, Taranto R, Schoetz DJ, Murray JJ, Coller JA. Inpatient *vs.* outpatient bowel preparation for elective colorectal surgery. *Dis Colon Rectum* 1996; **39**: 369–73.
6. Lawrance JA, Massoud TF, Creasy TS, Shatwell W, Mason A, Nolan DJ. Colonic preparation with Picolax: patient tolerance and approaches to fluid replacement. *Clin Radiol* 1994; **49**: 35–7.
7. Hill AG, Teo W, Still A, Parry BR, Plank LD, Hill GL. Cellular potassium depletion predisposes to hypokalaemia after oral sodium phosphate. *Aust N Z J Surg* 1998; **68**: 856–8.

Original article

Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation

F. Pi, F. Badosa*, A. Sola†, J. Roselló Catafau†, C. Xaus†, N. Prats‡, E. Gelpí† and G. Hotter†

Department of Surgery, Hospital de Viladecans, Institut Catala de la Salut and †Department of Medical Bioanalysis, Instituto de Investigaciones Biomédicas de Barcelona, Consejo Superior de Investigaciones Científicas–Instituto de Investigaciones Biomédicas August Pi i Sunyer, Barcelona and ‡Department of Animal Pathology, Veterinary School, Universidad Autonoma de Barcelona, Bellaterra, Spain, and *Department of Surgery, Albert Einstein Medical Center, Temple University of Medicine, Philadelphia, Pennsylvania, USA

Correspondence to: Dr G. Hotter, Department of Medical Bioanalysis, Instituto de Investigaciones Biomédicas de Barcelona, Consejo Superior de Investigaciones Científicas–Instituto de Investigaciones Biomédicas August Pi i Sunyer, C/Rosselló, 161, 7° planta, 08036 Barcelona, Spain (e-mail: ghcbam@iibb.csic.es)

Background: During cold preservation, cellular consumption of adenosine triphosphate leads to the accumulation of nucleotides and nucleosides. The precise role of adenosine in modulating the inflammatory response of cold-preserved pancreas after reperfusion remains to be elucidated. The aim of this study was to assess the influence of adenosine on the inflammatory response associated with the process of ischaemia–reperfusion in rat pancreas transplantation.

Methods: The effect of adenosine from preservation solution on the levels of high-energy nucleotides and their breakdown products after cold ischaemic preservation was determined. In addition, the inflammatory response associated with the process of ischaemia–reperfusion in pancreas transplantation was quantified with and without pretreatment with the adenosine antagonist theophylline, and during preservation of the organ in University of Wisconsin solution with and without adenosine.

Results: Adenosine from preservation solution is able to modify the nucleotide and nucleoside content of preserved pancreas, indicating that adenosine is incorporated and metabolized in tissue. Administration of the adenosine antagonist to transplanted rats moderated the increases in nitrite and nitrate, myeloperoxidase activity and lipoperoxidation levels in the pancreas.

Conclusion: Adenosine in the preservation solution may enhance the inflammatory response in rat pancreas transplantation.

Paper accepted 16 May 2001

British Journal of Surgery 2001, **88**, 1366–1375

Introduction

Ischaemia–reperfusion (I-R) after pancreas transplantation may increase the risk of graft pancreatitis, infection and vascular thrombosis[1]. The pathogenesis of I-R is multifactorial[2], involving vascular and endothelial damage, microcirculatory disturbances and white blood cell accumulation. All these factors need to be minimized or prevented to achieve successful grafting of the transplanted organ[3].

I-R following pancreas transplantation is characterized by capillary perfusion failure, activation of circulating leucocytes and loss of endothelial integrity with an accompanying increase in microvascular permeability[1]. It has been reported previously that alterations in the production of vasoactive substances such as eicosanoids[4], platelet activating factor[5] and nitric oxide play a key role in this process[6]. Nitric oxide, a ubiquitous signal transduction molecule, is a potent inducer of tissue injury because of its low molecular mass, free radical nature and diverse bioactivities[7]. In addition, nitric oxide production in other models of I-R seems to play an important role in minimizing the microvascular dysfunction associated with reperfusion[8].

During ischaemia, cellular consumption of adenosine 5′-triphosphate (ATP) leads to an accumulation of adenosine[9]. This product has been shown to protect against extended perfusion in cardiac transplantation[10]. Synthesized in the vascular endothelium and released into the surrounding vascular and interstitial compartments, adenosine may also be responsible for regulation of the inflammatory response.

The Editors have satisfied themselves that all authors have contributed significantly to this publication

In addition, it inhibits platelet activation and possesses potent antineutrophil properties including inhibition of neutrophil activity, homotypic aggregation, superoxide generation, and adhesion to the arterial and venous endothelium[11–13]. All these data suggest that the availability of adenosine as a substrate may be an important determinant of postischaemic metabolic and functional recovery of the pancreas subjected to I-R during transplantation. However, the exact role of adenosine in ischaemic tissues after reperfusion remains unclear.

Recent evidence also suggests that adenosine, by means of a receptor-mediated mechanism, stimulates the production of nitric oxide by endothelial cells[14], and that stimulation of nitric oxide production is dose dependent and present at physiological adenosine concentrations[15]. It has also been reported that nitric oxide can modulate adenosine release[16].

During pancreatic transplantation nitric oxide can induce an inflammatory response characterized by increased neutrophil recruitment[17]. Since adenosine is able to regulate the inflammatory response *per se* or through induction of nitric oxide synthesis, and as nitric oxide acts to induce injury in pancreas transplantation, this study was designed to determine the influence of exogenous adenosine on the modulation of nitric oxide synthesis and on the inflammatory response in the I-R syndrome associated with transplantation of the rat pancreas. To this end it was investigated whether adenosine in the preservation solution can be metabolized in tissue and is able to modify the nucleotide and nucleoside profile in the pancreas during preservation. The effects of adenosine antagonism on the development of the inflammatory response after reperfusion of the preserved graft were also studied.

Materials and methods

The study was performed with male Sprague–Dawley rats weighing 300–350 g (Ifa-Credo, Barcelona, Spain). Animals were anaesthetized with intraperitoneal 10 per cent urethane (Fluka, Buchs, Switzerland) (10 ml/kg) and placed in a supine position. All studies complied with the European Union regulations for experimental animals.

Isolation of the pancreas

Isolation of the pancreas was carried out through a median laparotomy, as described previously in experimental pancreas transplantations in the rat[18]. Animals were placed in the supine position on a heating pad to maintain body temperature between 36 and 37°C. The donor pancreas was procured from the donor rat by isolating the organ and its vascular supply from the aorta, including the superior mesenteric artery and coeliac axis as arterial inflow and the portal vein for venous outflow. The graft was flushed with 5 ml preservation solution and maintained at 4°C with a gauze soaked in cold saline, removed from the animal and immersed in preservation solution at 4°C.

Pancreatic transplantation

Pancreatic transplantation was carried out via a median laparotomy as described previously[18]. After isolation of the pancreas and immersion in preservation solution, the graft from the donor rat was placed in a heterotopic position and revascularized using the infrarenal segments of the vena cava and the aorta of the recipient. Both vessels were partially clamped for about 15 min. The graft was kept cold with gauze soaked in saline at 4°C. An end-to-side anastomosis was performed between the aortic segment of the graft and the aorta of the recipient, and similarly between the portal vein and the infrarenal vena cava of the recipient. Both anastomoses were performed using 9/0 polypropylene and 7/0 silk. The duodenum was removed from the pancreas by dividing the attached pancreas as closely as possible to the duodenum, before reperfusion.

Materials

Allopurinol, lactobionic acid, reduced glutathione, raffinose pentahydrate, potassium hydroxide and adenosine were from Sigma (St Louis, Missouri, USA). Hydroxyethyl starch was obtained as a pure powder from Elhoes, Fresenius (Hamburg, Germany) and University of Wisconsin solution (UW) was from Dupont Pharma (Bad Homburg, Germany). Modified UW (without adenosine) was prepared under controlled sterile conditions at the Central Pharmaceutical Service of the hospital. Solution was prepared freshly and used immediately.

Effect of adenosine on high-energy nucleotides in the preserved graft

To evaluate the effect of adenosine on high-energy nucleotides and their degradation products in pancreatic grafts, two groups of animals were studied. In group 1 the graft was flushed with 5 ml UW without adenosine (modified UW), and tissue samples were obtained after 0, 6 and 12 h of preservation ($n = 8$ for each timepoint). In group 2 the pancreatic graft was flushed with 5 ml UW and tissue samples were collected as for group 1 ($n = 8$ for each timepoint).

Tissue was used to evaluate the levels of ATP, adenosine 5′-diphosphate (ADP), adenosine 5′-monophosphate

(AMP), adenosine, inosine and xanthine by high-performance liquid chromatography (HPLC).

Effect of adenosine on the inflammatory response after reperfusion of the preserved graft

To evaluate the importance of adenosine in the development of the inflammatory response after transplantation a third group of rats was studied, which was subdivided into the following subgroups. (a) Control animals subjected to anaesthesia and laparotomy ($n = 6$). (b) Rats that underwent pancreas transplantation, with 12 h of donor organ preservation in UW at 4°C before revascularization in the recipient rat ($n = 8$). (c) Rats that underwent pancreas transplantation with 12 h of preservation in UW, but with administration of an adenosine antagonist before revascularization (theophylline pretreatment; 10 mg/ml intraperitoneally, a dose shown previously to be effective[19]); the donor rat was also pretreated with intraperitoneal theophylline 10 mg/ml before graft removal ($n = 8$). (d) As in subgroup (b) but pancreas preservation was done in modified UW ($n = 8$).

Blood and pancreatic tissue samples were obtained immediately in the control group and after 30 min of reperfusion in the other groups. Plasma lipase was evaluated as an index of pancreatic damage. The inflammatory response was measured by (1) the index of neutrophil recruitment, evaluated as myeloperoxidase (MPO) activity; (2) oxidative stress, evaluated as lipoperoxidation index (thiobarbiturate (TBA)-reactive substance); and (3) nitric oxide generation, evaluated as tissue nitrite and nitrate levels.

Biochemical assays

Nucleotide analysis

Samples of pancreas, weighing approximately 100–150 mg, were placed in 1·0 ml 3·6 per cent perchloric acid solution and homogenized immediately (S25N-8G; Labortechnik, Stauffen, Germany). Following homogenization, nucleotide and nucleoside levels were determined by HPLC as described previously[20].

Myeloperoxidase assay

MPO was measured photometrically using 3,3′,5,5′-tetramethylbenzidine as a substrate. Samples of pancreas were macerated with 0·5 per cent hexadecyltrimethylammonium bromide in phosphate buffer 50 mmol/l, pH 6·0. Homogenates were then disrupted for 30 s using a Labsonic (B. Braun, Melsungen, Germany) sonicator at 20 per cent power and subsequently snap-frozen in dry ice and thawed on three consecutive occasions before sonication for 30 s. Samples were incubated at 60°C for 2 h and then centrifuged at 4000*g* for 12 min. Supernatants were collected for MPO assay. Enzyme activity was assessed photometrically at 630 nm. The assay mixture consisted of 20 µl supernatant, 10 µl tetramethylbenzidine (final concentration 1·6 mmol/l) dissolved in dimethylsulphoxide, and 70 µl hydrogen peroxide (final concentration 3·0 mmol/l) diluted in phosphate buffer 80 mmol/l, pH 5·4. An enzyme unit was defined as the amount of enzyme that produces an increase of 1 absorbance unit per min[20].

Lipoperoxidation

Lipid peroxidation was determined by the TBA reaction, measuring the formation of malondialdehyde (TBA-reactive substance). Some 2 ml 20 per cent trichloroacetic acid was added to 2 ml homogenate. After mixing and centrifuging, 1 ml TBA water solution (0·67 per cent) was added to the supernatant and boiled for 60 min. After cooling, optical density at 530 nm was measured[21].

Lipase assay

Lipase activity was measured in heparinized blood plasma using a commercial kit (Boehringer, Mannheim, Germany), according to the supplier's instructions.

Nitric oxide production

Nitric oxide production in pancreatic tissue was determined by tissue accumulation of nitrite and nitrate, using a modification of a method described elsewhere[22]. Briefly, frozen tissue specimens were homogenized in 3 ml Tris-hydrochloride 100 mmol/l, pH 4·0, at 4°C. Homogenates (2 ml) were centrifuged at 100 000*g* for 60 min and 200 µl of each supernatant was transferred to 1·5-ml Eppendorf tubes. Nitrate was reduced to nitrite with 0·5 units nitrate reductase in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) 50 µmol/l and flavine adenine dinucleotide (FAD) 5 µmol/l. The excess of NADPH was oxidized in the presence of pyruvate 0·2 mmol/l and 1 µg lactate dehydrogenase. Nitrite was determined with Greiss reagent by adding sulphanilic acid 1 mmol/l and hydrochloric acid 100 mmol/l. After incubation for 5 min tubes were centrifuged and 150 µl supernatant was transferred to a 96-well microtitre plate. After a first reading of the absorbance at 595 nm, 50 µl naphthylenediamine was added. After 15 min of incubation the absorbance was compared against a sodium nitrite standard.

Protein measurement

Total protein concentration in pancreatic homogenates was determined using a commercial kit (Bio-Rad, Munich, Germany).

Histological study

Samples of pancreas were fixed in 10 per cent neutral buffered formalin, paraplast embedded, cut into 5-μm sections and stained with haematoxylin and eosin following standard procedures. The sections were evaluated by light microscopy.

Statistical analysis

Data are expressed as mean(s.e.m.) and were evaluated statistically by analysis of variance, followed by Student–Newman–Keuls test. $P < 0{\cdot}05$ was considered to be significant.

Results

Effect of adenosine from the preservation solution on high-energy nucleotides and their breakdown products in the preserved graft

Fig. 1 shows the total content of high-energy nucleotides and nucleosides (ATP, ADP, AMP, adenosine, inosine, hypoxanthine and xanthine) after various preservation periods. The total content of high-energy nucleotides and their breakdown products remained constant at all times. However, significant increases in the total content were observed in tissues preserved in UW compared with those preserved in the modified UW.

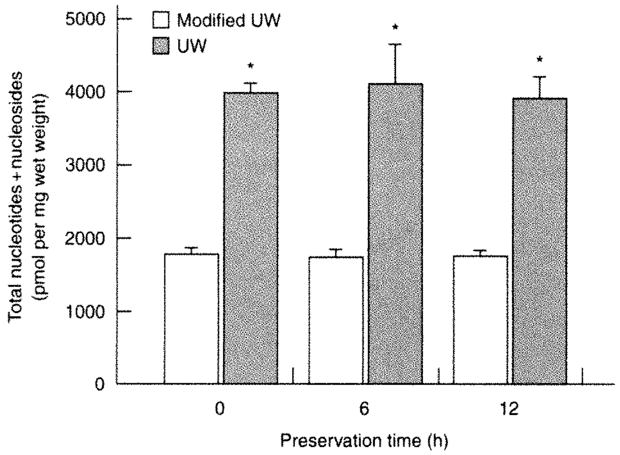


Fig. 1 Mean(s.e.m.) total nucleotide and nucleoside content (adenosine 5′-triphosphate + adenosine 5′-diphosphate + adenosine 5′-monophosphate + adenosine + inosine + xanthine) in pancreatic grafts flushed and preserved with University of Wisconsin solution (UW) or modified UW for 0, 6 and 12 h. $^*P < 0{\cdot}05$ *versus* modified UW (Student Newman Keuls test)

Fig. 2 shows the tissue levels of ATP, ADP, AMP, adenosine, inosine and hypoxanthine/xanthine after the different preservation periods evaluated in this study. In the two solutions studied, levels of ATP and ADP decreased steadily as a function of the duration of preservation. Levels of AMP, adenosine, inosine and hypoxanthine/xanthine increased initially, and remained stable between 6 and 12 h of preservation. Significant increases in levels of AMP, adenosine, inosine and hypoxanthine/xanthine were seen in grafts preserved in UW compared with levels in grafts preserved in solution without adenosine (modified UW).

Effect of adenosine from the preservation solution on the inflammatory response after reperfusion of the preserved graft

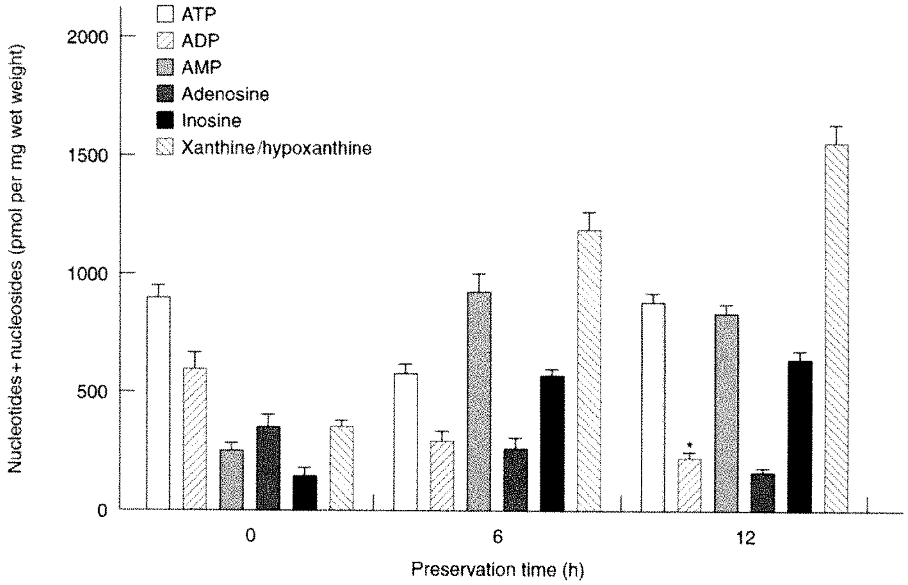
To evaluate the role of exogenous adenosine on the development of the tissue inflammatory response after pancreas transplantation, the effects of administration of the adenosine antagonist theophylline on this response were studied.

Transplantation (using UW as preservation solution) induced an increase in the levels of TBA-reactive substance and MPO in tissue in comparison with the control group (*Fig. 3*). This increase was prevented by administration of theophylline before transplantation, or when the pancreas was preserved with the preservation solution without adenosine.

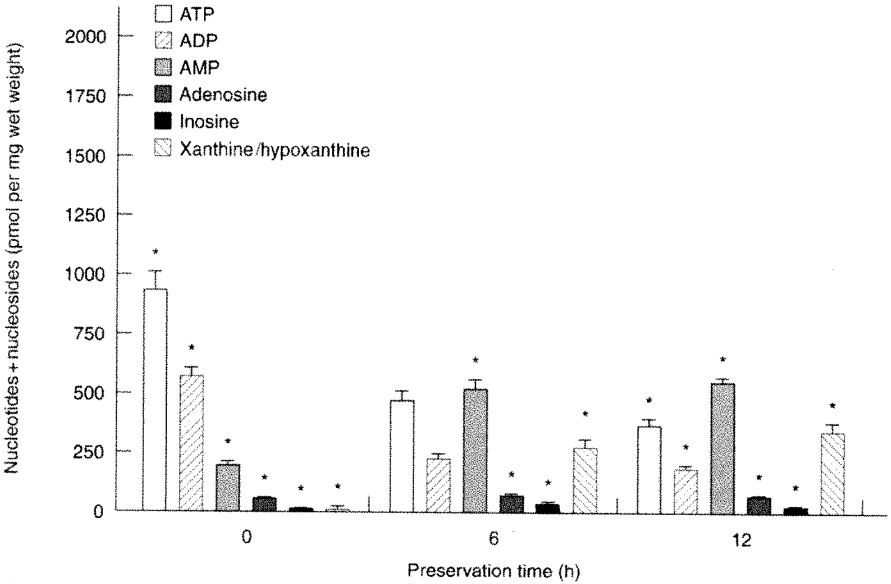
Increased levels of lipase were observed after transplantation using UW as preservation solution, but administration of theophylline or preservation without adenosine reduced lipase levels (*Fig. 4*).

Fig. 5 shows the levels of nitric oxide in tissue, evaluated as nitrite and nitrate production. Increased levels were observed after transplantation using UW, whereas pretreatment with theophylline or preservation without adenosine had no effect on nitric oxide production in pancreatic grafts.

The histological findings confirmed the biochemical results (*Fig. 6*). Lesions observed in the transplanted group consisted of margination and adherence of polymorphonuclear (PMN) leucocytes to the endothelium of interstitial small vessels (*Fig. 6b*, arrowhead) and PMN leucocyte perivascular infiltration (*Fig. 6c*, arrowhead). In contrast, lesions in the group treated with theophylline were minimal and consisted of a small number of PMN leucocytes around interstitial vessels (*Fig. 6d*, arrows). The same minimal lesions were observed in the transplanted group in which preservation solution without adenosine was used (*Fig. 6e*). In all the transplanted groups slight interstitial oedema and very small focal areas of pancreatic necrosis were seen.



a UW



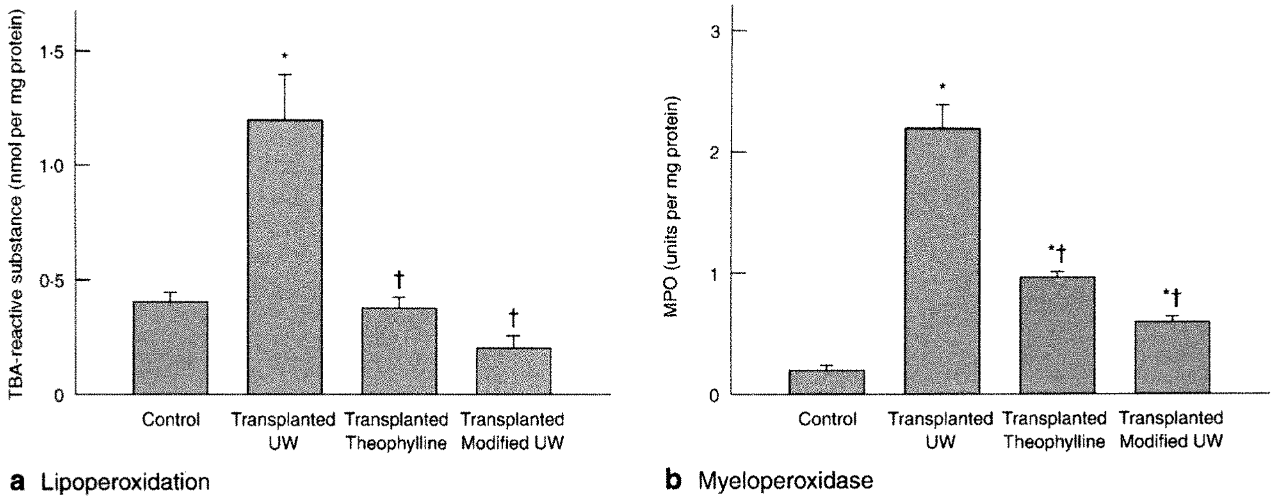
b Modified UW

Fig. 2 Mean(s.e.m.) adenosine 5′-triphosphate (ATP), adenosine 5′-diphosphate (ADP), adenosine 5′-monophosphate (AMP), adenosine, inosine and xanthine/hypoxanthine levels in pancreatic grafts flushed and preserved with **a** University of Wisconsin solution (UW) or **b** modified UW for 0, 6 and 12 h. $^*P < 0.05$ *versus* UW (Student Newman Keuls test)

Discussion

Simultaneous pancreas–kidney transplantation has become a standard procedure in patients with type I diabetes mellitus and endstage renal disease[23]. However, graft pancreatitis is still a major problem, and I-R injury is an important event in the pathogenesis of this condition. Endothelial dysfunction, with the development of perivascular oedema and neutrophil adhesion, is found very early in the I-R injury of the pancreas.

Adenosine is reported to be one of the inflammatory mediators involved in regulating I-R injury[24]; it may



a Lipoperoxidation

b Myeloperoxidase

Fig. 3 Mean(s.e.m.) **a** lipoperoxidation levels and **b** myeloperoxidase (MPO) activity in pancreatic tissue from controls; rats transplanted with donor organ subjected to 12 h of preservation in University of Wisconsin solution (UW) and 30 min of reperfusion; transplanted rats pretreated with theophylline; and rats transplanted with donor organ subjected to 12 h of preservation in modified UW. *$P < 0.05$ *versus* control; †$P < 0.05$ *versus* transplanted UW group (Student Newman Keuls test)

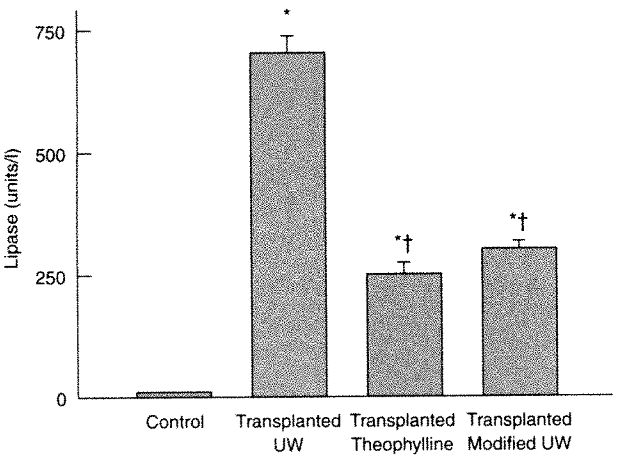


Fig. 4 Mean(s.e.m.) lipase levels in plasma corresponding to the following groups: controls; rats transplanted with donor organ subjected to 12 h of preservation in University of Wisconsin solution (UW) and 30 min of reperfusion; transplanted rats pretreated with theophylline; and rats transplanted with donor organ subjected to 12 h of preservation in modified UW. *$P < 0.05$ *versus* control; $^{\dagger}P < 0.05$ *versus* transplanted UW group (Student Newman Keuls test)

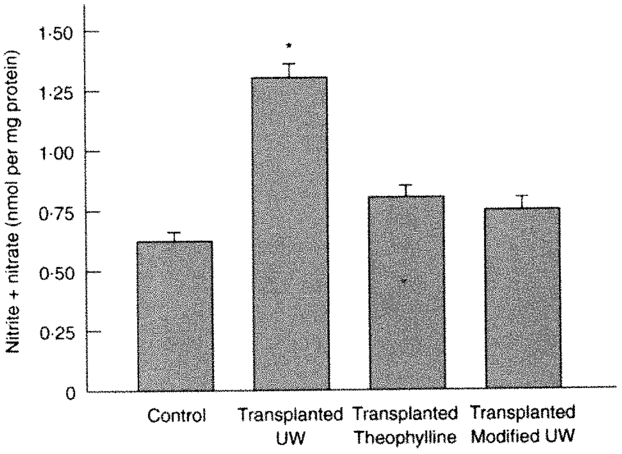
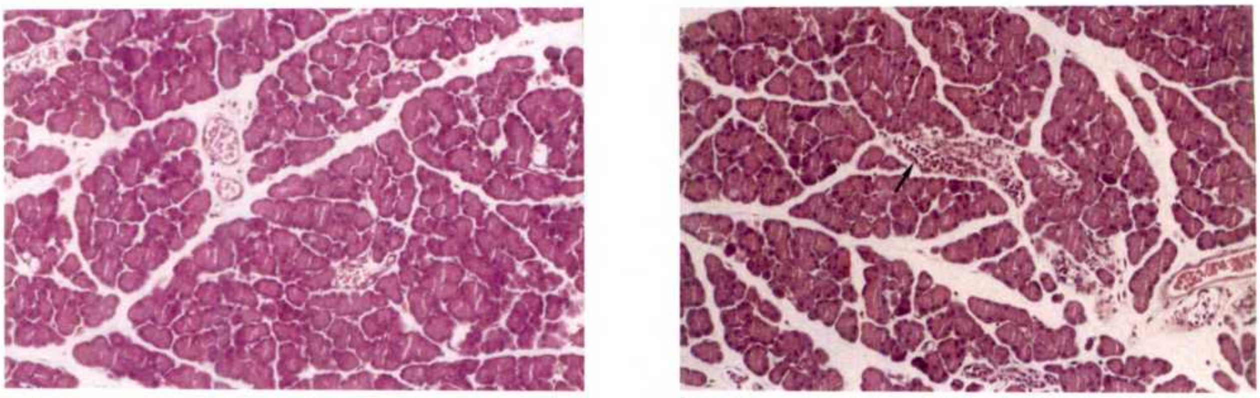


Fig. 5 Mean(s.e.m.) nitrite + nitrate levels in pancreatic tissue corresponding to the following groups: controls; rats transplanted with donor organ subjected to 12 h of preservation in University of Wisconsin solution (UW) and 30 min of reperfusion; transplanted rats pretreated with theophylline; and rats transplanted with donor organ subjected to 12 h of preservation in modified UW. *$P < 0.05$ *versus* control (Student Newman Keuls test)

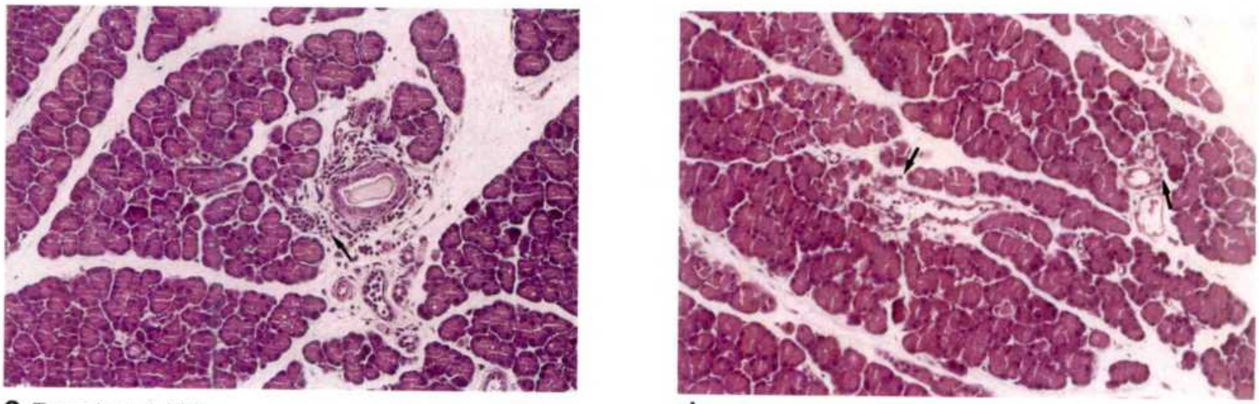
prevent some of the effects of the I-R injury associated with transplantation procedures[24–26]. In addition, adenosine has been shown to mediate various biological actions such as increased blood flow, vasodilatation, inhibition of free radical production, suppression of neutrophil activation and prevention of platelet aggregation[27,28]. The deleterious effect of adenosine was also described by Raschke and Becker[29]; administration of a selective adenosine antagonist prevented functional injury by neutrophils in a heart I-R model.

The adenosine contained in UW provides the preserved cells with substrates for the regeneration of ATP during the



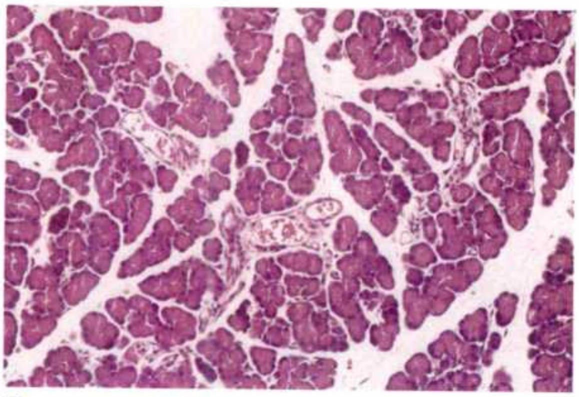
a Control

b Transplanted, UW



c Transplanted, UW

d Transplanted, theophylline



e Transplanted, modified UW

Fig. 6 Histological lesions of the pancreas (representative of the mean of eight qualitative observations per group). **a** Control group; **b** and **c** group transplanted with donor organ subjected to 12 h of preservation in University of Wisconsin solution (UW) and 30 min of reperfusion; **d** transplanted rats with theophylline pretreatment; **e** group transplanted with donor organ subjected to 12 h of preservation in modified UW (haematoxylin and eosin stain; original magnification × 215)

reperfusion period following cold storage[25], but adenosine is also produced endogenously by the breakdown of ATP nucleotides during ischaemia[30]. While it has been shown that enhancement of endogenous adenosine attenuates the ischaemic cardiac[31] and liver[32] injury, fewer studies have addressed the role of adenosine in pancreas preservation. Adenosine in UW-preserved tissues may come from two potential sources: it may be an initial constituent of UW, or it may be formed by degradation of ATP during ischaemia. To ascertain whether adenosine in the preservation solution could modify tissue adenosine content after preservation, the adenosine content in tissues preserved in UW was compared with that found in tissues preserved in UW without adenosine (modified UW). Preservation of the pancreas in UW led to a significant increase in the total nucleotide and nucleoside content compared with preservation in modified UW. This indicates that adenosine from the preservation solution may be able to modify the tissue metabolism of high-energy nucleotides.

The kinetics of adenine nucleotide degradation and corresponding appearance of nucleosides followed a similar pattern in the two solutions studied. In general terms, ATP and ADP levels showed a tendency to decrease as a function of the length of the preservation period, whereas AMP, adenosine, inosine and hypoxanthine/xanthine showed a constant steady increase. In addition, levels of adenosine, inosine and hypoxanthine/xanthine were higher in UW-preserved tissues than in tissues preserved in the solution without adenosine. The higher percentage of adenosine in the UW-preserved pancreas indicates that adenosine from the preservation solution is incorporated into the tissue. On the other hand, the accumulation of hypoxanthine/xanthine and inosine indicates that adenosine is partly metabolized to its degradation product, hypoxanthine/xanthine, which enhances superoxide anion formation by xanthine oxidase.

The accumulation of xanthine could act as a trigger for the production of oxygen free radicals during reperfusion, since pharmacological interventions aimed at decreasing this substrate of xanthine oxidase can decrease the severity of the injury in canine models of global ischaemia and reflow[33]. In addition, it has been shown that administration of adenine nucleotides is potentially harmful if they are degraded during ischaemia, leading to the production of greater amounts of hypoxanthine and, therefore, increased generation of oxygen free radicals during reperfusion[34].

The effect of an increased concentration of xanthine in the UW-preserved pancreas may be reduced by the action of allopurinol, a xanthine oxidase inhibitor[35,36], also present in UW. While the increased content of nucleotides may have beneficial effects, the increased hypoxanthine/xanthine formation may lead to harmful effects, but the role of nucleotide and nucleoside content in preservation has not been evaluated in this study. Adenosine appears to be a key component in UW[25,37,38], since its supply to the graft during preservation stimulates ATP synthesis and improves the viability of the ischaemically damaged pancreas[25,38]. It has also been shown to reduce the release of toxic oxygen metabolites from neutrophils[11], serving as an endogenous modulator of superoxide anion generation. However, adenosine stimulates nitric oxide production by endothelial cells[14], and nitric oxide may also act as an inducer of the inflammatory response after pancreas transplantation[6,17] since nitric oxide inhibition is able to induce the release of endothelin and neutrophil recruitment[17]; this may well indicate that enhanced adenosine levels during pancreas preservation also increase the subsequent inflammatory response.

The present study also investigated the role of the presence of adenosine in regulating the inflammatory response in early reperfusion. The results indicate that adenosine in rat pancreas transplantation increases oxidative stress and the recruitment of neutrophils after the reperfusion of the preserved pancreas, suggesting that in these experimental conditions adenosine enhances the inflammatory response of the pancreas. This is supported by the observation that administration of the adenosine antagonist theophylline or preservation in UW without adenosine decreased lipoperoxidation and neutrophil recruitment in the pancreas, evaluated in this study as TBA-reactive substance formation and MPO activity. The histological results also confirmed the action of adenosine as an inducer of the inflammatory response. There was minimal neutrophil infiltration in the pancreas preserved in UW without adenosine (*Fig. 6e*) or in the antagonist-treated group (*Fig. 6d*), compared with the increased neutrophil recruitment in transplants preserved in UW.

The fact that use of UW without adenosine had the same effect on the inflammatory response as theophylline pretreatment indicates that the observed effects may be attributed to the reduced adenosine and not to theophylline-specific effects. One of the ways in which adenosine in UW may enhance the inflammatory response is via its action on nitric oxide release. As observed in *Fig. 5*, preservation in UW without adenosine or administration of adenosine antagonist to transplanted rats resulted in decreased levels of nitric oxide generation in pancreatic tissue. This result indicates that adenosine enhances the inflammatory response in pancreatic transplantation, and in addition enhances nitric oxide release; however, a cause–effect relationship can be suggested only tentatively, as other mechanisms of action of adenosine may be responsible for this inflammatory action.

Among the possible mechanisms that may contribute to the inflammatory actions of adenosine, accumulated xanthine (a consequence of adenosine metabolism) could act as an inducer of the inflammatory response. In this case, the transplanted group treated with theophylline allowed discrimination of the effects of adenosine only from those resulting from xanthine.

It is clear that the UW is highly efficient for pancreas transplantation[25] and in clinical conditions[39]. Several studies have investigated which components of UW are essential for successful preservation of the pancreas[40]. The aim of this study was to determine whether the presence of adenosine in the preservation solution affects the inflammatory response in early reperfusion, and whether the introduction of adenosine antagonists may prevent this early inflammatory response. The findings suggest that adenosine may act as an inducer of the inflammatory response in early reperfusion after pancreas transplantation.

References

1 Kusterer K, Poschmann T, Friedemann A, Enghofer M, Zendler S, Usadel KH. Arterial constriction, ischemia–reperfusion, and leukocyte adherence in acute pancreatitis. *Am J Physiol* 1993; **265:** G165–71.

2 Winchell RJ, Halasz NA. Lack of effect of oxygen-radical scavenging systems in the preserved reperfused rabbit kidney. *Transplantation* 1989; **48:** 393–6.

3 Lefer AM, Lefer DJ. Pharmacology of the endothelium in ischemia–reperfusion and circulatory shock. *Annu Rev Pharmacol Toxicol* 1993; **33:** 71–90.

4 Hotter G, Leon OS, Roseló-Catafau J, Lopez-Boado MA, Paralleda PP, Henriques RD *et al.* Tissular prostanoid release, phospholipase A_2 activity, and lipid peroxidation in pancreas transplantation. *Transplantation* 1991; **51:** 987–90.

5 Pi F, Hotter G, Closa D, Rosello-Catafau J, Bulbena O, Basoda F *et al.* Effect of platelet-activating factor antagonist and desferroxamine administration on eicosanoid production in rat pancreas transplantation. *Transplantation* 1994; **57:** 12–17.

6 Hotter G, Closa D, Pi F, Prats N, Fernandez Cruz L, Bulbena O *et al.* Nitric oxide and arachidonate metabolism in ischemia–reperfusion associated with pancreas transplantation. *Transplantation* 1995; **59:** 417–21.

7 Matheis G, Sherman MP, Buckberg GD, Haybron DN, Young HH, Ignarro LJ. Role of L-arginine–nitric oxide pathway in myocardial reoxygenation injury. *Am J Physiol* 1992; **262:** H616–20.

8 Aoki N, Johnson G III, Lefer AM. Beneficial effects of two forms of NO administration in feline splanchnic artery occlusion shock. *Am J Physiol* 1990; **258:** G275–81.

9 Smits P, Williams SB, Lipson DE, Banitt P, Rongen GA, Creager MA. Endothelial release of nitric oxide contributes to the vasodilator effect of adenosine in humans. *Circulation* 1995; **92:** 2135–41.

10 Petsikas D, Mohamed F, Ricci M, Symes J, Guerraty A. Adenosine enchances left ventricular flow during 24-hour hypothermic perfusion of isolated cardiac allografts. *J Heart Transplant* 1990; **9:** 543–7.

11 Cronstein BN, Daguma L, Nichols D, Hutchison AJ, Williams M. The adenosine/neutrophil paradox resolved: human neutrophils posses both A1 and A2 receptors that promote chemotaxis and inhibit O_2 generation, respectively. *J Clin Invest* 1990; **85:** 1150–7.

12 Cronstein BN, Levin RI, Belanoff J, Weissmann G, Hirschhorn R. Adenosine: an endogenous inhibitor of neutrophil-mediated injury to endothelial cells. *J Clin Invest* 1986; **78:** 760–70.

13 Cronstein BN, Naime D, Ostad E. The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an *in vivo* model of inflammation. *J Clin Invest* 1993; **92:** 2675–82.

14 Li JM, Fenton RA, Cutler BS, Dobson JG Jr. Adenosine enhances nitric oxide production by vascular endothelial cells. *Am J Physiol* 1995; **269:** C519–23.

15 Maekawa K, Saito D, Obayashi N, Uchida S, Haraoka S. Role of endothelium-derived nitric oxide and adenosine in functional myocardial hyperemia. *Am J Physiol* 1994; **267:** H166–73.

16 Fischer H, Prast H, Philippu A. Adenosine release in the ventral striatum of the rat is modulated by endogenous nitric oxide. *Eur J Pharmacol* 1995; **275:** R5–6.

17 Hotter G, Pi F, Sanz C, Peralta C, Prats N, Gelpí E *et al.* Endothelin mediated nitric oxide effects in ischemia–reperfusion associated with pancreas transplantation. *Dig Dis Sci* 1998; **43:** 2627–33.

18 Lee S, Tung KS, Koopmans JG, Chandler JG, Orloff MJ. Pancreaticoduodenal transplantation in the rat. *Transplantation* 1972; **13:** 421–5.

19 Martinez-Tica JF, Zornow MH. Effects of adenosine agonists and an antagonist on excitatory transmitter release from the ischemic rabbit hippocampus. *Brain Res* 2000; **872:** 110–15.

20 Peralta C, Closa D, Xaus C, Gelpí E, Roselló-Catafau J, Hotter G. Hepatic preconditioning is defined by a balance of adenosine and xanthine. *Hepatology* 1998; **28:** 768–73.

21 Hotter G, Closa D, Prats N, Pi F, Gelpí E, Roselló-Catafau J. Free radical enhancement promotes leukocyte recruitment through a PAF and LTB_4 dependent mechanism. *Free Radic Biol Med* 1997; **22:** 947–54.

22 Hortelano S, Genaro AM, Boscá L. Phorbol esters induce nitric oxide synthase activity in rat hepatocytes. Antagonism with the induction elicited by lipopolysaccharide. *J Biol Chem* 1992; **267:** 24 937–40.

23 Büsing M, Martin D, Riege R, Schulz T, Dehof S, Kozuschek W. Combined pancreas/kidney transplantation as standard procedure in therapy of type I diabetic patients in renal failure. *Chirurg* 1996; **67:** 1002–6.

24 Fremes SE, Zhang J, Furukawa RD, Mickle DA, Weisel RD. Adenosine pretreatment for prolonged cardiac storage. An evaluation with St Thomas' Hospital and University of Wisconsin solutions. *J Thorac Cardiovasc Surg* 1995; **110:** 293–301.

25 Southard JH, van Gulik TM, Ametani MS, Vreugdenhil PK, Lindell SL, Pienaar BL *et al.* Important components of the UW solution. *Transplantation* 1990; **49:** 251–7.

26 Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; **46:** 235–47.

27 Ward PA, Cunningham TW, McCulloch KK, Johnson KJ. Regulatory effects of adenosine and adenine nucleotides on oxygen radical responses of neutrophils. *Lab Invest* 1988; **58:** 438–47.

28 McKie LD, Bass BL, Dunkin BJ, Harmon JW. Nitric oxide mediates the blood flow response to intravenous adenosine in the rabbit. *Circ Shock* 1994; **43:** 103–6.

29 Raschke P, Becker BF. Adenosine and PAF dependent mechanisms lead to myocardial reperfusion injury by

neutrophils after brief ischaemia. *Cardiovasc Res* 1995; **29**: 569–76.

30 Smits P, Williams SB, Lipson DE, Banitt P, Rongen GA, Creager MA. Endothelial release of nitric oxide contributes to the vasodilator effect of adenosine in humans. *Circulation* 1995; **92**: 2135–41.

31 Fremes SE, Furukawa RD, Zhang J, Li RK, Tumiati LC, Weisel RD *et al.* Cardiac storage with University of Wisconsin solution and a nucleoside-transport blocker. *Ann Thorac Surg* 1995; **59**: 1127–33.

32 Todo S, Zhu Y, Zhang S, Jin MB, Ishizaki N, Tanaka H *et al.* Attenuation of ischemic liver injury by augmentation of endogenous adenosine. *Transplantation* 1997; **63**: 217–23.

33 Xia Y, Zweier JL. Substrate control of free radical generation from xanthine oxidase in the postischemic heart. *J Biol Chem* 1995; **270**: 18 797–803.

34 Paller MS, Hoidel JR, Ferris TF. Oxygen free radicals in ischemic acute renal failure in the rat. *J Clin Invest* 1984; **74**: 1156–64.

35 Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. 2nd ed. Oxford. Clarendon Press, 1989.

36 Peters SM, Rauen U, Tijsen MJ, Bindels RJ, van Os CH, de Groot H *et al.* Cold preservation of isolated rabbit proximal tubules induces radical-mediated cell injury. *Transplantation* 1998; **65**: 625–32.

37 Hiraoka K, Kuroda Y, Tanioka Y, Matsumoto S, Fujino Y, Morita A *et al.* Adenosine is a key component in preservation of ischemically damaged canine pancreas by the two-layer cold storage method. *Transplant Proc* 1994; **26**: 953–5.

38 Fujino Y, Kuroda Y, Morita A, Tanioka Y, Ku Y, Saitoh Y. The effect of fasting and exogenous adenosine on ATP tissue concentration and viability of canine pancreas grafts during preservation by the two-layer method. *Transplantation* 1993; **56**: 1083–6.

39 Belzer FO, D'Alessandro AM, Hoffmann RM, Knechtle SJ, Reed A, Pirsch JD *et al.* The use of UW solution in clinical transplantation. A 4-year experience. *Ann Surg* 1992, **215**: 579–83.

40 Urushihara T, Sumimoto R, Suminmoto K, Jamieson NV, Ito H, Ikeda M *et al.* A comparison of some simplified lactobionate preservation solutions with standard UW solution and Eurocollins solution for pancreas preservation. *Transplantation* 1992; **53**: 750–4.

Original article

Reintervention as a clinical trial endpoint after peripheral arterial bypass surgery

H. R. Watson, G. Belcher* and M. Horrocks

Department of Medical Sciences, University of Bath, Bath and *Takeda Europe Research and Development Centre, London, UK
Correspondence to: Dr H. R. Watson, Pharmacia Medical Development, PO Box 53, Lane End Road, High Wycombe HP12 4HL, UK
(e-mail: hugh.watson@pharmacia.com)

Background: Graft patency is usually the primary endpoint in studies of peripheral arterial bypass surgery, but gives only a limited indication of clinical outcome. The aim of this study was to evaluate reintervention as a study endpoint after femorodistal bypass surgery.

Methods: The database from a multicentre, prospectively planned study of 517 patients undergoing femorodistal bypass for severe ischaemia was used to investigate the predictive value of technical endpoints. Clinical symptoms, graft patency, vascular interventions and clinical outcomes were recorded for 12 months after operation.

Results: Complete follow-up data were obtained on 498 patients (96 per cent). Success in terms of patients' need for reintervention agreed with clinical outcome in 90 (95 per cent confidence interval (c.i.) 87–93) per cent of cases. Primary and secondary patency agreed with the clinical outcome in 80 (95 per cent c.i. 77–84) and 81 (95 per cent c.i. 78–85) per cent of patients respectively. However, the best agreement with clinical outcome was obtained from the composite endpoint of 'patient alive without reintervention': 92 (95 per cent c.i. 90–94) per cent.

Conclusion: Recording the number of patients who did not need reintervention for 12 months after femorodistal bypass gave a more accurate assessment of the number with clinical improvement than was obtained by recording bypass graft patency. Inclusion of patient survival in a composite endpoint increased the clinical relevance of this endpoint in patients with severe ischaemia who had femorodistal bypass surgery.

Paper accepted 27 May 2001

British Journal of Surgery 2001, **88**, 1376–1381

Introduction

Reports of studies on peripheral arterial bypass procedures commonly include a number of outcome measures including primary and secondary graft patency and amputation rate. All are useful and represent different aspects of the overall clinical picture. However, statistical hypothesis testing in comparative studies requires the identification of a single primary endpoint. The question then arises as to which endpoint is the most important or clinically relevant.

Analysis of the primary graft patency rate is generally used as the principal assessment of the technical success of the initial peripheral bypass procedure. Secondary patency provides a measure of the cumulative technical success of surgical efforts to provide a blood supply to a leg. However, it has been demonstrated that even secondary graft patency is not always a reliable guide to clinical outcome[1] and there is a growing awareness that patency alone provides insufficient information to compare outcomes in peripheral bypass surgery[2].

An advantage of using patency, primary or secondary, as a trial endpoint is that it can be determined objectively; assessment of symptom severity is inevitably more subjective, depending on information elicited from the patient. To be more useful than graft patency, an endpoint should be clear and objectively verifiable, as well as being relevant to patient's symptoms.

As some patients have a successful outcome despite an occluded bypass, one option would be to establish the number of patients who underwent reintervention to improve blood flow after the initial procedure. The number of patients free from intervention might be expected to provide a good indication of the proportion who had a good clinical outcome. Using this variable, operations in patients whose bypass remained patent for long enough to allow a lasting improvement in the clinical situation could be classified as successful even if the bypass subsequently occluded. Further options for obtaining a more accurate assessment of the number of patients with a clinical improvement would be to use compound endpoints encompassing both technical and clinical variables. The database from a large, prospectively planned trial[3] was analysed in order to establish how well different endpoints agreed with the clinical outcome.

Patients and methods

Patients were studied prospectively in a trial of adjuvant pharmacotherapy in femorodistal bypass procedures[3]. The patients all had arterial bypass surgery for severe ischaemia with the proximal anastomosis above the knee and the distal anastomosis below the knee, principally to the tibioperoneal trunk, the anterior tibial, posterior tibial or peroneal arteries.

Before surgery all patients were classified as having grade III or IV peripheral arterial occlusive disease according to the Fontaine classification. Twelve months after operation patients were reclassified according to Fontaine grade: grade I was defined as no symptoms of ischaemia in the relevant leg, grade II as intermittent claudication, grade III as ischaemic rest pain and/or the use of analgesics to control rest pain, and grade IV as the presence of ischaemic ulcers or gangrene with or without rest pain. Bypass graft patency was recorded at the same intervals as clinical symptoms and was confirmed by angiography or duplex ultrasonography if necessary.

Assessment of clinical symptoms and bypass graft patency for each patient was based on the limb operated on entry into the study; only one reconstruction per patient was included. All surgical or catheter procedures performed in the same leg as the initial femorodistal bypass were recorded for 12 months. Amputations of toes or the forefoot were classified as minor amputations, and those above the ankle (below knee, through or above knee) were classified as major amputations.

The following reinterventions in the relevant leg were included: any intervention intended to maintain or restore patency of the original bypass, any new bypass in the same leg, and any amputation above the ankle. Amputations or other interventions in the other leg were not included. Minor amputations in the ipsilateral leg were also not included in this analysis as many were planned at the time of the femorodistal bypass, but performed shortly afterwards.

The outcome at 12 months was calculated for a number of different technical and composite endpoints. Technical endpoints were calculated according to the following definitions: primary patency (patency without reintervention following the initial bypass procedure), secondary patency (patency with or without reintervention) and intervention free (the patient did not need any surgical or catheter intervention in the ipsilateral leg following the initial bypass procedure).

Composite technical and clinical endpoints were calculated according to the following definitions: patient alive with an intact leg and primary patency (patient alive without a major amputation and with primary patency of the bypass graft), patient alive with an intact leg and secondary patency (patient alive without a major amputation and with secondary patency of the bypass graft) and patient alive without reintervention (patient alive without any surgical or catheter intervention in the ipsilateral leg following the initial bypass procedure).

The extent to which the different technical and composite endpoints were associated with a good clinical outcome was investigated by comparison with the clinical outcome at 12 months. Good clinical outcome was defined as Fontaine grades I or II at 12 months; poor clinical outcome was defined as Fontaine grades III or IV, or a major amputation.

Patients were included in each analysis when the relevant information on (1) patency or vascular interventions and (2) clinical outcome was available. In the case of the composite endpoints where death was included as a component, all patients were included, no outcome being interpreted as death and a poor clinical outcome. The calculations of agreement between the various endpoints and clinical outcome were based on absolute numbers of patients.

Considering the clinical outcome to be the correct result, the false-positive and false-negative rates that would have resulted from using each of the technical and composite endpoints as the primary endpoint were calculated. The extent of the agreement of the different endpoints with clinical outcome was compared using the percentage of patients with agreement and 95 per cent confidence intervals.

Results

Five hundred and seventeen patients underwent femorodistal bypass and were included in the study. Data on both clinical outcomes and bypass patency at 12 months were available on 498 patients (96 per cent), of whom 419 had not undergone amputation or died before graft occlusion and could be included in the comparison of patency rates with clinical outcome. Information on both clinical outcomes and reinterventions was available for 414 patients who had not died before reintervention and could therefore be included in the comparison of reintervention rate and clinical outcome.

Vascular interventions performed

A total of 426 reinterventions were performed in the relevant leg in 239 patients in the first 12 months after the initial femorodistal bypass procedure (*Table 1*). The majority of these patients underwent a thrombectomy or other surgical revision of the graft owing to occlusion or threatened occlusion. A smaller number of patients received a completely new bypass graft in the same leg. One or more percutaneous angioplasties were performed in 16 patients, of whom seven also underwent other procedures.

Table 1 Frequency of different types of reintervention

Surgical procedure	No. of procedures	No. of patients (n = 517)
Angioplasty of graft stenosis	18	16 (3·1)
Thrombectomy of graft	78	67 (13·0)
Operative revision of graft	126	101 (19·5)
New bypass graft	30	30 (5·8)
Minor amputation	57	50 (9·7)
Major amputation	117	108 (20·9)
Total	426	239 (46·2)
Total excluding minor amputations	369	215 (41·6)

Values in parentheses are percentages

Twenty-four of the patients (5 per cent) underwent only a minor amputation and no other reinterventions in the relevant leg. The major amputations consisted of 83 below-knee amputations and revisions, and 34 above- or through-knee amputations and revisions. Nine patients (2 per cent) underwent two major amputations on the same leg. The percentage of patients who had any reintervention was high, irrespective of the bypass technique and material used (*Table 2*).

Technical endpoints

The extent to which the intervention-free rate represents the patients with a good clinical outcome was recorded for the 414 patients who survived to 12 months or who had a vascular procedure before that (*Fig. 1*). A total of 236 patients was intervention free, but 41 of these had a poor clinical outcome at 12 months. These 41 patients could be considered as false positives if being intervention free was

Table 2 Rate of reintervention by bypass procedure with and without major amputations

		Number with interventions	
Bypass procedure	n	Excluding amputations	Including amputations
In situ saphenous vein	292	81 (28 (23–33))	115 (39 (33–45))
Reversed saphenous vein	90	23 (26 (17–35))	30 (33 (23–43))
Polytetrafluoroethylene	62	21 (34 (22–46))	29 (47 (35–59))
Vein–prosthetic composite	29	5 (17 (3–31))	11 (38 (20–56))
Vein–vein composite	42	18 (43 (28–58))	22 (52 (37–67))

Values in parentheses are percentages (95 per cent confidence intervals)

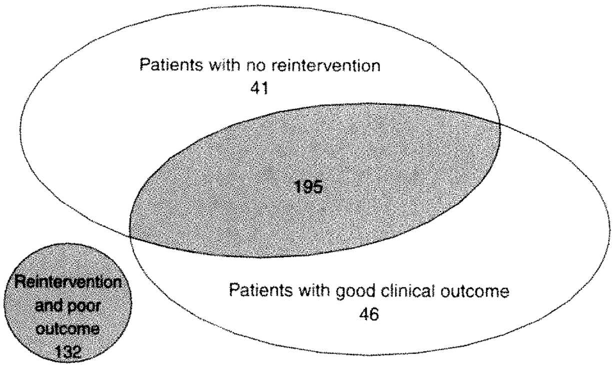

Patients with no reintervention
41
195
Reintervention and poor outcome
132
Patients with good clinical outcome
46

Fig. 1 Concordance of patients with no reintervention and clinical outcome at 12 months. Shading represents concordance between technical and clinical outcome (n = 414)

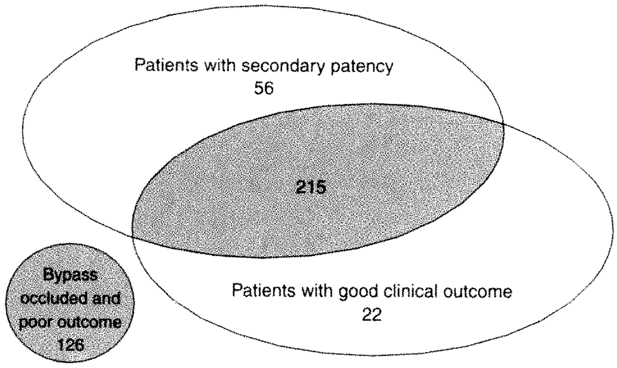

Patients with secondary patency
56
215
Bypass occluded and poor outcome
126
Patients with good clinical outcome
22

Fig. 2 Concordance of patients with secondary patency and a good clinical outcome at 12 months. Shading represents concordance between technical and clinical outcome (n = 419)

interpreted as indicating a good clinical outcome, a false-positive rate of 10 per cent.

A small proportion of the reinterventions were indicated by the development of graft stenoses. All of these patients reported persisting or recurrent symptoms, in addition to satisfying haemodynamic criteria for the intervention. An intervention performed for an asymptomatic stenosis could have been considered a false-negative result in that the patient would not actually have had an adverse clinical outcome at the time of the reintervention. However, there were no false negatives, as the interventions in all 178 patients were indicated by a poor clinical outcome to the initial bypass procedure, even if 46 of the patients subsequently had a good outcome. There was therefore a concordance of reintervention as an endpoint with the clinical outcome from the initial operation in 90 per cent of patients.

This was compared with the concordance of primary and secondary patency with clinical outcome; for primary patency a false-positive rate of 7 per cent, a false-negative rate of 13 per cent and a concordance of 80 per cent were found. The respective figures for secondary patency were 13, 5 and 81 per cent (*Fig. 2*).

Combined technical and clinical outcome measures

The number of patients in whom the composite endpoint agreed with the clinical outcome was tabulated for patients alive without reintervention, patients alive with an intact leg and primary patency, and patients alive with an intact leg and secondary patency (*Table 3*).

The endpoint 'patient alive without reintervention' showed a false-positive rate of 41 of 517 patients (8 per cent) (*Fig. 3*). There were, in effect, no false negatives as it was assumed, as with reintervention alone, that all 46 patients undergoing a reintervention and having a good outcome would otherwise have had a poor outcome.

The false-positive rate was lower for 'patient alive with an intact leg and primary patency' at 28 of 517 (5 per cent), but higher for 'patient alive with an intact leg and secondary patency' at 56 of 517 (11 per cent) (*Fig. 4*). This was balanced in these two composites endpoints by respective

Table 3 Rates of false positive and false negative observed using various technical and composite endpoints as surrogates for good clinical outcome

Endpoint	*n*	False positive (%)	False negative (%)	Concordance (%)
Primary patency	419	7 (4–9)	13 (10–16)	80 (77–84)
Secondary patency	419	13 (10–17)	5 (3–7)	81 (78–85)
With no reintervention	414	10 (7–13)	0	90 (87–93)
Alive with an intact leg and primary patency	517	5 (4–7)	10 (8–13)	84 (81–87)
Alive with an intact leg and secondary patency	517	11 (8–14)	4 (3–6)	85 (82–88)
Alive without reintervention	517	8 (6–10)	0	92 (90–94)

Values in parentheses are 95 per cent confidence intervals

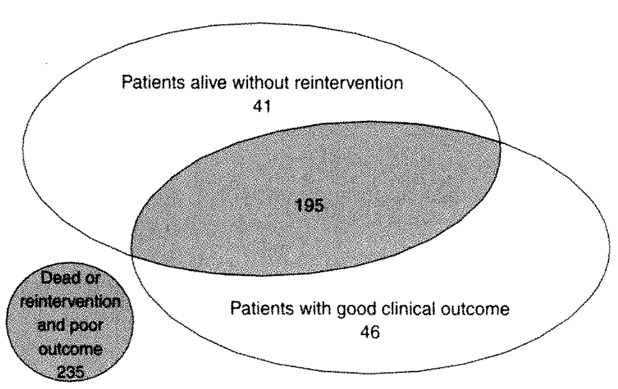

Patients alive without reintervention
41
195
Dead or reintervention and poor outcome
235
Patients with good clinical outcome
46

Fig. 3 Concordance of 'patient alive without reintervention' and clinical outcome at 12 months. Shading represents concordance between technical and clinical outcome ($n = 517$)

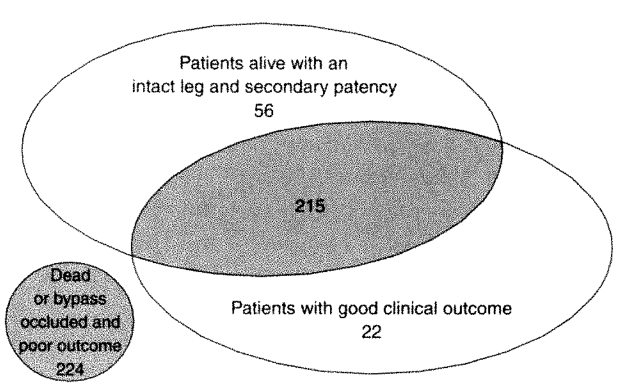

Patients alive with an intact leg and secondary patency
56
215
Dead or bypass occluded and poor outcome
224
Patients with good clinical outcome
22

Fig. 4 Concordance of 'patient alive with an intact leg and secondary bypass patency' and clinical outcome at 12 months. Shading represents concordance between technical and clinical outcome ($n = 517$)

false-negative endpoint rates of 54 of 517 (10 per cent) and 22 of 517 (4 per cent).

Comparison of different endpoints

The false-positive and false-negative rates that occurred taking each of the various technical and composite endpoints as surrogates for clinical outcome (measured by Fontaine grade) are summarized in *Table 3*. The best overall concordance of endpoint and clinical outcome was obtained with patients who had no reintervention or were 'alive without reintervention'. Excluding patients who only had angioplasty of a graft stenosis from the intervention group did not improve the concordance of these endpoints with clinical outcome.

Discussion

The concept of a single primary endpoint for a clinical trial conforms to widely accepted statistical principles. This can be a single variable or a composite endpoint resulting from the summation or combination of several variables or discrete categories, but it should be well defined *a priori*, and clinically relevant.

Clinical trials in peripheral bypass surgery usually report bypass patency as the primary endpoint[4]. However, considerable discrepancies between patency rates and clinical outcome have been reported[5] and it has been suggested that additional information on the clinical outcome should be given in all studies dealing with leg ischaemia[6]. Unfortunately, a patient's symptoms are largely subjective, making it difficult to incorporate them into an objective endpoint, so other indicators of clinical outcome should be considered.

The most commonly reported clinical outcomes in this field are leg and patient survival, both of which are easy to record. These endpoints are most useful in patients with advanced disease and those undergoing distal reconstructive procedures who are at highest risk of amputation or death. However, they do not provide any information on the outcome in patients who retain their legs. In this study, reintervention rates were compared with patency rates as a measure of clinical outcome in patients with leg survival.

The value of recording reinterventions in the relevant leg is that they reflect either a deterioration, or lack of improvement in the symptoms following the initial bypass. The time to reintervention could also provide a measure of the duration of symptom improvement after a bypass. Although this is a technical endpoint, it would be expected to *reflect* clinical symptoms as opposed to patency, which is a technical endpoint expected to *determine* symptoms.

An overlap of patients without reintervention and those with primary patency would be expected, but not every patient with a bypass graft occlusion requires reintervention and, conversely, some patients with a patent bypass undergo reintervention owing to lack of clinical improvement.

One drawback in taking the intervention-free rate as an indication of technical and clinical success is that some patients who do not have reintervention could be in need of a further operation but, by virtue of their general state of health or the lack of feasibility of further procedures, reintervention is not undertaken. Analysis of this database suggested that this might apply to approximately 10 per cent of the patients who underwent distal bypass, those who were classified as false positives. Furthermore, the judgement of different surgeons as to whether or not a further procedure is appropriate will not always produce the same answer. The surgeon has to consider a number of factors: the condition of the affected leg, the patient's clinical status, the choice of procedure and graft material, the cause and time interval of graft failure, and the likely durability of the reoperation[7]. This element of subjectivity would be problematic in any trial that was not double blind, as surgeons may be biased towards intervening. This was not an issue in the study analysed here as reintervention had not been selected as a primary endpoint.

The classification of procedures for rescuing a threatened graft as reinterventions could theoretically result in patients who have improved symptoms being classified as failures. However, in this study, all the patients who had pre-emptive procedures also had severe ischaemic symptoms before the procedure. It is possible that some surgeons might be reluctant to intervene except when a perceived haemodynamic threat to the graft is accompanied by a poor clinical status.

Allowing for the inclusion or exclusion of amputations in other studies, similar rates of reintervention to those reported in this study have been described in several other studies of bypass surgery for leg ischaemia[8–11], suggesting that the series of patients used in this analysis was not unusual. It seems logical to include major amputations in a composite endpoint, as these also represent a failure of the bypass procedure and a worsening of symptoms. The case for including minor amputations is not so clear. A distal bypass may be performed with no expectation of avoiding a toe or metatarsal amputation, but a minor amputation might also at other times represent a failure of the initial bypass. The decision taken in the present study was that the patient could have a good clinical outcome despite having had a minor amputation, so this was not interpreted as a failure.

The concordance of intervention-free status with a good clinical outcome according to Fontaine grade was greater than it was for the endpoints of primary or secondary bypass patency. An additional value of recording interventions is that they are an important component of healthcare costs. The information of interest would be not only the time to first intervention but also the number and type of each intervention, as interventions differ widely in cost.

Composite endpoints incorporating not only a technical component but also clinical components such as death or major amputation resulted in a marginally better agreement with clinical outcome than the technical endpoints alone. Since patients who died or had a major amputation before graft occlusion would be censored under conventional life-table analysis, including all patients in a composite endpoint analysis would conform more closely to analysis according to the intention-to-treat principle. The disadvantage is that such an analysis would give the impression of low surgical success rates compared with results analysed in the conventional manner. It does, however, accurately record the number of patients who had an overall satisfactory result of 'alive with an intact leg and patent bypass' or 'alive with no reintervention'. It could be argued that only this result represents the correct choice of operation coupled with a good technical result.

The optimal solution for peripheral bypass graft trials may be to report a composite endpoint as outlined above, which in practice equates to counting the number of patients at the end of follow-up who survive with an intact leg and a patent bypass, or who survive and are intervention free. If a single rather than a composite endpoint is preferred, analysis of patients who are intervention free gives a closer approximation to the clinical results.

The current practice of reporting bypass graft patency by life-table analysis assumes that missing data are random, but this has been shown not to be the case[12]. Composite endpoints have the additional advantage that results can be quoted as the absolute numbers of patients with a positive outcome, since there is no censoring owing to death or amputation. These endpoints lend themselves well therefore to analysis according to the intention-to-treat principle.

One limitation of the data presented here is that the patients all had severe ischaemia and underwent a distal bypass procedure. Patients with claudication might be less likely to undergo reintervention in the case of failure of the initial bypass. It would be important to know the severity of symptoms before surgery before comparing reintervention rates in two patient groups to avoid any bias. The value of reintervention as an endpoint should ideally be evaluated in a group of patients with intermittent claudication undergoing reconstructive surgery.

Acknowledgements

The authors acknowledge the help of Professor J. A. Dormandy (St George's Hospital, London) in reviewing this paper and contributing to the discussion.

References

1 Watson HR, Schroeder TV, Simms MH, Buth J, Horrocks M, Norgren L *et al.* Relationship of femorodistal bypass patency to clinical outcome. Iloprost Bypass International Study Group. *Eur J Vasc Endovasc Surg* 1999; **17**: 77–83.

2 Dawson I, Van Bockel JH. Outcome measures after lower extremity bypass surgery: there is more than just patency. *Br J Surg* 1999; **86**: 1105–6.

3 Iloprost Bypass International Study Group. Effects of perioperative iloprost on patency of femorodistal bypass grafts *Eur J Vasc Endovasc Surg* 1996; **12**: 363–71.

4 Watson HR, Belcher G, Horrocks M. Adjuvant medical therapy in peripheral bypass surgery. *Br J Surg* 1999, **86**: 981–91.

5 Nicoloff AD, Taylor LMJ, McLafferty RB, Moneta GL, Porter JM. Patient recovery after infrainguinal bypass grafting for limb salvage. *J Vasc Surg* 1998; **27**: 256–63.

6 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; **26**: 517–38.

7 Rutherford RB. Selection of patients for reoperation for failed reconstruction. *Acta Chir Scand Suppl* 1987; **538**: 24–30.

8 Swedish Society for Vascular Surgery. Reoperations, redo surgery and other interventions constitute more than one third of vascular surgery. A study from Swedvasc (the Swedish Vascular Registry) *Eur J Vasc Endovasc Surg* 1997; **14**: 244–51.

9 Dawson I, van Bockel JH. Reintervention and mortality after infrainguinal reconstructive surgery for leg ischaemia. *Br J Surg* 1999, **86**: 38–44.

10 Lawson JA, Tangelder MJD, Algra A, Eikelboom BC, on behalf of the Dutch BOA Study Group. The myth of the *in situ* graft superiority in infrainguinal bypass surgery? *Eur J Vasc Endovasc Surg* 1999; **18**: 149–57.

11 Cheshire NJW, Noone MA, Wolfe JHN. Re-intervention after vascular surgery for critical leg ischaemia. *Eur J Vasc Surg* 1992; **6**: 545–50.

12 Jensen LP, Nielsen OM, Schroeder TV. The importance of complete follow-up for results after femoro-infrapopliteal vascular surgery. *Eur J Vasc Endovasc Surg* 1996; **12**: 282–6.

Outcome of surgical treatment for carotid body paraganglioma

J. T. M. Plukker, E. P. Brongers, A. Vermey, A. Krikke* and J. J. A. M. van den Dungen†

Departments of Surgical Oncology/Head and Neck Surgery, *Radiology and †Vascular Surgery, University Hospital Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands
Correspondence to: Dr J. T. M. Plukker (e-mail: j.th.plukker@chir.azg.nl)

Background: The present study reviewed a 30-year experience of managing carotid body paraganglioma (CBP) and analysed clinical findings associated with perioperative morbidity.
Methods: Clinical records, radiological findings and pathological reports of all patients who presented with CBP between 1966 and 1997 were reviewed. There were 39 consecutive patients with 45 tumours and median follow-up was 10 years. The Shamblin classification was used to define complication rates and long-term surgical results.
Results: Preoperative information derived from magnetic resonance angiography (MRA) and colour Doppler imaging (CDI) was comparable to that from standard four-vessel arteriography. Forty-one CBPs were resected in 35 patients. Six patients had bilateral tumours and seven had multicentric tumours. The median duration of operation and blood loss were substantially higher for Shamblin type III tumours. All major vascular complications (four of 39 patients) and permanent neurological complications (three of 39) were observed in type III tumours.
Conclusion: Surgical planning and prediction of perioperative complications can be obtained by staging derived from MRA and CDI. Severe complications occur predominantly in type III CBPs.

Paper accepted 27 May 2001

British Journal of Surgery 2001, **88**, 1382–1386

Introduction

Paragangliomas are non-chromaffin tumours that originate from paraganglionic cells migrating from the neural crest in close relation with autonomic ganglion cells. These rare, slow-growing tumours are usually found during the fourth and fifth decades of life, and are equally distributed between the sexes[1–7]. More than 80 per cent are located in the head and neck. The two main groups are cervical (carotid and vagal) and skull base (jugular and tympanic) paragangliomas[1]. The first group is more accessible to surgery; tumours at the jugular foramen are more complex. Carotid body paragangliomas (CBPs) encroach upon and gradually encase the carotid bulb. Moreover, they may extend along the carotid artery involving adjacent cranial nerves including the vagus, hypoglossal and glossopharyngeal nerves, and the sympathetic chain[1,3–8]. Surgery is the most effective treatment. Meticulous subadventitial dissection can be performed with acceptable morbidity; however, this procedure may be difficult, with the risk of bleeding or damage to adjacent neurovascular structures[9,10]. Stroke and cranial nerve palsy, the most frequently observed major complications, are closely related to the size of the tumour and are reported after 12–40 per cent of operations[7,11–13]. The use of carotid intraluminal shunting and preoperative selective angiographic embolization to facilitate surgery and to diminish blood loss are controversial[8,10,14,15].

In a dissertation at the University of Groningen, Elders[2] presented the results of 50 patients with CBP who were treated between 1945 and 1960. The tumour was only biopsied in ten patients. Of the 33 complete resections, 12 patients had one or more serious complications; eight had severe vascular damage (hemiplegia) and seven had cranial nerve injuries. At that time resection was not recommended in patients over 70 years and for tumours greater than 5 cm. The present study analysed the results of the periadventitial dissection technique adopted since that period, and assessed the effect of tumour size and vascular invasion on the complication rate.

Patients and methods

The medical records of 63 patients (42 women and 21 men) with an extra-adrenal paraganglioma treated at the University Hospital Groningen between 1966 and 1997 were reviewed. The group included 39 patients (62 per cent) with a CBP. There were also 17 patients (27 per cent) with a jugulotympanic paraganglioma, five patients (8 per cent) with a vagal paraganglioma, one with an aortic paraganglioma and one with a paraganglioma located in the retroperitoneum. Before 1967, preoperative angiography was performed by direct puncture of the carotid artery, but more recently digital subtraction angiography or magnetic resonance angiography (MRA) has been used. Based on this information the tumours were classified according to Shamblin and Linder to predict the difficulty at surgery[16–18]. Shamblin type I tumours are small with minimal arterial attachment. Type II tumours are usually larger; they exhibit moderate arterial attachment and partially surround both carotid arteries. Type III tumours are characterized by encasement of the carotid bifurcation. Subadventitial excision was performed in all surgically treated patients, and complete follow-up was available. The clinical presentation, diagnostic procedures and perioperative management were related to the results of resection and complications. Vocal cord function was recorded before and after operation by laryngoscopic examination.

Surgical procedure

A curved horizontal skin incision of 10–12 cm was made 4–5 cm beneath the mandibular arch. After exposure of the common, internal and external carotid arteries as well as the vagal and hypoglossal nerves, the carotid arteries were controlled by vessel loops (*Fig. 1*), as described by Gordon-Taylor in 1940[16]. Meticulous dissection in the subadventitial plane was performed in all patients; occasionally novocaine was injected in this cleavage plane to facilitate the surgical procedure. In large tumours or when there was extensive arterial invasion, the external carotid artery (ECA) was sacrificed to avoid excessive bleeding and to mobilize the tumour posteriorly from the internal carotid artery (ICA). Tumours extending cranially were better exposed by dividing the digastric and stylomastoid muscle with mobilization of the parotid gland.

Results

Thirty-nine patients with a median age of 43 (range 11–83) years underwent surgery. There were 25 women and 14 men. Median follow-up was 10 (range 3–22) years. The tumour was familial in ten patients; these were usually bilateral or combined with a jugulotympanic paraganglioma. In two patients the tumour was malignant as proven by nodal involvement and bone metastases. The most common preoperative sign was a slowly enlarging cervical mass at the level of the carotid bifurcation (36 of 39 patients), which was fixed in the vertical plane, but mobile horizontally. Pulsatile sensations were felt by ten patients. Four presented with a cranial nerve palsy including hoarseness in three and hypoglossal dysfunction in one patient. The median duration between onset of symptoms and diagnosis of CBP was 15 (range 1–120) months. Before admission the tumour was explored or biopsied in another hospital in 12 patients.

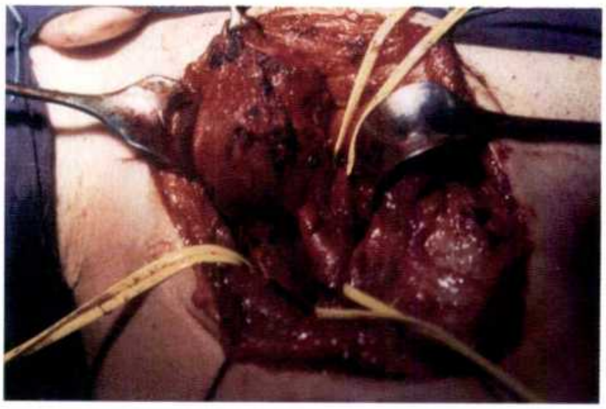


Fig. 1 During resection of a type III carotid body paraganglioma with vessel loops around the three main vessels

Imaging

Angiography confirmed the clinical diagnosis in 37 of 39 patients. Other imaging techniques introduced sequentially since 1974 were computed tomography (eight patients), magnetic resonance imaging (seven) and colour Doppler imaging (CDI) in the last five patients. Tumour diagnosis and extension were correctly determined by MRA/CDI in all these latter patients. These modalities are the current imaging techniques used at this institution for suspected CBP. A total of 45 CBPs were identified in the 39 patients, 21 on the left and 24 on the right. Six patients had bilateral paragangliomas and multicentricity was observed in seven patients. Extension could be determined before operation in 34 tumours by grading the encasement of both the ICA and ECA, to predict the operative difficulty. Five patients had a type I CBP, a small and relatively easily resectable tumour. Twenty-one tumours were adherent to and partially surrounding the carotid arteries (type II). Eight tumours encased the carotid vessels and frequently included transmural invasion (type III).

Surgical treatment

Four patients declined or were not offered surgery owing to advanced age or poor health. In the remaining 35, 41 CBPs were completely resected. The mean duration of operation was 2·9 (range 1·5–7·5) h; it was 2·0, 2·5 and 4·5 h for type I, II and III CBPs respectively. The mean blood loss was 750

Table 1 Complications after surgery for carotid body paraganglioma according to stage of tumour

Shamblin type	*n*	Mean diameter (cm)	Mean duration of surgery (h)	Mean blood loss (l)	Vascular complications	Neurological complications
I	5	3·0	2·0	0·40	–	–
II	21	4·1	2·5	0·72	2 minor	3 temporary
III	8	6·6	4·5	2·20	4 major 1 minor	3 paralysis 2 temporary

(range 50–4600) ml, and was lowest in type I (400 ml) and highest in type III (2200 ml) tumours. The diameter of the tumours ranged from 3 to 10 cm with a mean size of 3·0, 4·1 and 6·6 cm in Shamblin type I, II and III lesions respectively (*Table 1*). No patient died after surgery. During follow-up, no patient developed local recurrence, but metastatic disease was noted in two patients.

Complications

Vascular injuries occurred frequently during excision of Shamblin type III CBPs. The ECA had to be resected in 14 tumours, seven of which were type III (seven of eight). The ICA was injured in seven of 41 operations. One patient, who was initially explored elsewhere, recovered from a postoperative hemiplegia after resection of the tumour with ligation of the ICA without reconstruction. A minor lesion of the arterial wall was repaired simply in two patients, but reconstruction of the ICA was required in four other patients. Saphenous vein patch was used for reconstruction in three patients (two at reintervention) and an 8-mm Dacron (Du Pont, Stevenage, UK) interposition graft was used in the fourth. All four major vascular injuries that required reconstruction occurred in patients with type III tumours. During follow-up, all reconstructed ICAs remained patent. One patient with bilateral CBP and jugulotympanic paragangliomas became blind in one eye after resection of the second primary CBP, probably owing to thromboembolism.

Cranial nerve injuries were observed in eight patients of whom five had Shamblin type III tumours. These injuries involved the cervical sympathetic trunk (Horner's syndrome; $n = 4$), the hypoglossal nerve ($n = 5$) and the vagal nerve ($n = 5$). In five patients the cranial nerve dysfunction was temporary and recovered within 5 months after surgery.

The complication rates following resection were not related to the age of the patients. The procedure was uneventful in eight of the ten patients aged over 50 years. Of the other two, both with type III CBPs, one needed reconstruction of a damaged ICA and in the other the hypoglossal nerve was injured.

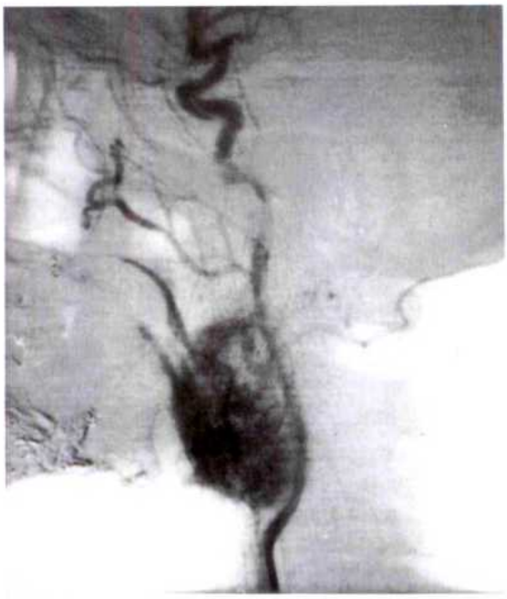


Fig. 2 Highly vascularized carotid body paraganglioma with characteristic tumour blush and broadening of the carotid bifurcation demonstrated on carotid angiography

Discussion

The estimated incidence of CBP in the Netherlands is 0·06 per 100 000. Assessment of the extent of vascular involvement by four-vessel cerebral imaging and MRA of both carotid and vertebral arteries is essential in the treatment of these highly vascular tumours. Accumulation of contrast with widening of the carotid bifurcation and shifting of the ICA posterolaterally and the ECA anteromedially is characteristic (*Fig. 2*). Besides information on location and extension, MRA can detect multicentric or bilateral tumours. Multicentric tumours occurred in seven of 39 patients in this study and the CBP was familial in ten patients. It should be distinguished from metastatic malignant paraganglioma, which was found in two patients with resected tumours[3–7,9,17].

CBPs are limited to the adventitia of the carotid artery, so a meticulous subadventitial dissection, according to

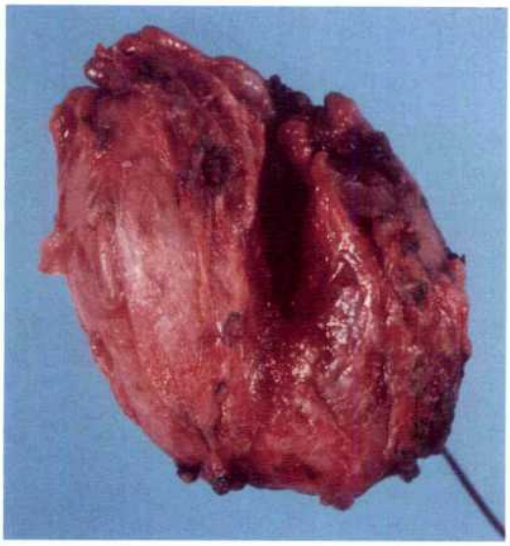


Fig. 3 Resected type III carotid body paraganglioma

Gordon-Taylor[16], is the most appropriate treatment. To remove these tumours entirely from the encased ICA, they must be cleaved dorsolaterally (*Fig. 3*). Contemporary vascular reconstruction techniques may contribute to better surgical treatment. ICA occlusion causes stroke in approximately 30 per cent of patients and intraluminal shunting is advocated when the carotid artery has to be clamped[13,19,20]. Adequate planning using the Shamblin (Mayo Clinic) classification[17], based on the size and involvement of the carotid vessels, can predict the risk of surgery in CBPs. Tumours encircling both the ICA and ECA were adherent to the carotid wall to such an extent that complete resection was often necessary with arterial shunting and vascular reconstruction. ICA damage in these type II/III tumours was greater because of severe invasion and friability of the vessel wall. Therefore Shamblin type III tumours should be treated by a surgical team with vascular experience in carotid shunting and graft replacement. The median size of tumours requiring such an approach was 6·6 cm, similar to the diameter of 6 cm in the series of Pantanowitz *et al.*[21]. Vascular complications might be reduced by preoperative examination of collateral cerebral cross-flow. Intraoperative monitoring of middle cerebral artery blood flow with transcranial Doppler still needs further evaluation.

Preoperative selective embolization remains controversial. Proponents argue that embolization facilitates the surgical procedure and reduces blood loss[8,11,22], while others found a relatively increased risk of stroke[23,24]. In a recent study of 32 CBPs, one of the six patients had a procedure-related stroke after selective embolization[25]. These authors advocated preoperative embolization for tumours larger than 3–5 cm. However, in a group of 23 patients studied over 10 years, Litle *et al.*[26] presented an experience of 11 tumours (median size 4–5 cm) that were embolized before operation and found no difference in blood loss or in duration of surgery. The mean blood loss and duration of operation in the present study did not differ from those after embolization recorded in the literature[22,24,25]. Owing to revascularization oedema and local inflammatory responses after embolization, surgery is advised within 48 h[9,14].

The rate of major vascular complications including stroke has dropped from 30 per cent before 1960 to less than 1 per cent in the current literature. In this series only one patient had a severe vascular problem after ligation of the ICA. The latter should be abandoned nowadays owing to the high risk of hemiplegia (more than 20 per cent). There are no preoperative measurements that could be used to identify patients in whom the ICA could be clamped or ligated safely. The injured ICA should be reconstructed with a saphenous vein patch or interposition graft. For tumours extending up to the base of the skull, dislocation of the temporomandibular joint may be useful. ECA resection enables mobilization of tumours adherent to the posterior side of the carotid bifurcation.

The risk of cranial nerve palsy is between 13 and 56 per cent. Vagal, hypoglossal, glossopharyngeal and sympathetic nerves are frequently involved in Shamblin type II/III tumours. Cranial nerve palsy occurred in ten patients in this study. Most of these patients had a type III CBP (*Table 1*). These results are comparable with a stroke rate of 2 per cent and nerve injury rate of 29 per cent in a collection of 177 patients treated between 1986 and 1990[27]. To minimize the risk of complications subadventitial dissection should be performed at an early stage. Surgery can then be carried out with less bleeding and without selective embolization. Arterial replacement or an intraluminal shunt may be required, particularly in advanced type III lesions.

References

1 Glenner GG, Grimley PM. Tumors of the extra-adrenal paraganglion system (including chemoreceptors). Introduction: historical background and terminology. In: *Atlas of Tumour Pathology*. 2nd series, fascicle 9. Washington, DC: Armed Forces Institute of Pathology, 1974: 13–16.

2 Elders RAR. Paraganglioma. Een overzicht en bespreking van 92 Nederlandse patienten. *Thesis*, University of Groningen, 1962.

3 Lack EE, Cubilla AL, Woodruff JM, Farr HW. Paragangliomas of the head and neck region: a clinical study of 69 patients. *Cancer* 1977; **39:** 397–409.

4 van Asperen de Boer FRS, Terpstra JL, Vink M. Diagnosis,

treatment and operative complications of carotid body tumours. *Br J Surg* 1981; **68:** 433–8.

5 Dickinson PH, Griffin SM, Guy AJ, McNeill IF. Carotid body tumour: 30 years experience. *Br J Surg* 1986; **73:** 14–16.

6 Padberg FT, Cady B, Persson AV. Carotid body tumor. The Lahey Clinic experience. *Am J Surg* 1983; **145:** 526–8.

7 McPherson GAD, Halliday AW, Mansfield AO. Carotid body tumours and other cervical paragangliomas: diagnosis and management in 25 patients. *Br J Surg* 1989; **76:** 33–6.

8 Robison JC, Shagets FW, Beckett WC, Spies JB. A multidisciplinary approach to reducing morbidity and operative blood loss during resection of carotid body tumor. *Surg Gynecol Obstet* 1989; **168:** 166–70.

9 LaMuraglia GM, Fabian RL, Brewster DC, Pile-Spellman J, Darling RC, Cambria RP *et al.* The current surgical management of carotid body paragangliomas. *J Vasc Surg* 1992; **6:** 1038–45.

10 Smith RF, Shetty PC, Reddy DJ. Surgical treatment of carotid paragangliomas presenting unusual technical difficulties. The value of preoperative embolization. *J Vasc Surg* 1988; **7:** 63–7.

11 Muhm M, Polterauer P, Gstottner W, Temmel A, Richling B, Undt G *et al.* Diagnostic and therapeutic approaches to carotid body tumors. Review of 24 patients. *Arch Surg* 1997; **132:** 279–84.

12 Bastounis E, Maltezos C, Pikoulis E, Leppaniemi AK, Klonaris C, Papalambros E. Surgical treatment of carotid body tumours. *Eur J Surg* 1999; **165:** 198–202.

13 Hallett JW, Nora JD, Holler LH, Cherry KJ, Pairolero PO. Trends in neurovascular complications of surgical management for carotid body and cervical paragangliomas: a 50 year experience with 153 tumors. *J Vasc Surg* 1988; **7:** 284–91.

14 Schick PM, Hieshma GB, White RA, Fiaschetti FL, Mehringer CM, Grinnell VS *et al.* Arterial catheter embolization followed by surgery for large chemodectoma. *Surgery* 1980; **84:** 459–64.

15 Borges LF, Heros RC, De Brun G. Carotid body tumors managed with preoperative embolization. *J Neurosurg* 1983; **59:** 867–70.

16 Gordon-Taylor G. On carotid tumours. *Br J Surg* 1940; **28:** 163–72.

17 Shamblin WR, ReMine WH, Sheps SG, Harrison EG. Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. *Am J Surg* 1971; **122:** 732–9.

18 Linder F, Wagner M, Allenberg J, Koffler M. Tumoren des Glomus caroticum: Klinik und forschung. *Chirurg* 1984; **55:** 19–24.

19 Rosen IB, Palmer JA, Golberg M, Mustard RA. Vascular problems associated with carotid body tumors. *Am J Surg* 1981; **142:** 459–63.

20 Javid H, Chawla SK, Dye WS, Hunter JA, Najafi H, Goldin MD *et al.* Carotid body tumor: resection or reflection. *Arch Surg* 1976; **111:** 344–7.

21 Pantanowitz D, Pitts-Davidge K, Demetriades D. The significance of carotid bifurcation angle in carotid body tumours. *S Afr Med J* 1991; **80:** 318–21.

22 Tikkakoski T, Luotonen J, Leinonen S, Siniluoto T, Heikkila O, Paivansalo M *et al.* Preoperative embolization in the management of neck paragangliomas. *Laryngoscope* 1997; **107:** 821–6.

23 Brackman D, Kinney S, Fu K. Glomus tumor: diagnosis and management. *Head Neck Surg* 1987; **9:** 306–11.

24 Murphy TP, Brackman DE. Effects of pre-operative embolisation on glomus jugulare tumors. *Laryngoscope* 1989; **99:** 1244–7.

25 Westerband A, Hunter GC, Cintora I, Coulthard SW, Hinni ML, Gentile AT *et al.* Current trends in the detection and management of carotid body tumors. *J Vasc Surg* 1998; **28:** 84–92.

26 Litle VR, Reilly LM, Ramos TK. Preoperative embolization of carotid body tumors: when is it appropriate? *Ann Vasc Surg* 1996; **10:** 464–8.

27 Williams MD, Phillips MJ, Nelson WR, Rainer WG. Carotid body tumor. *Arch Surg* 1992; **127:** 963–8.

Original article

Small bowel obstruction after appendicectomy

R. E. B. Andersson

Department of Surgery, Ryhov Hospital, S-551 85, Jönköping, Sweden
Correspondence to: Dr R. E. B. Andersson (e-mail: roland.andersson@ryhov.ltjkpg.se)

Background: This study analysed the risk of surgically treated small bowel obstruction after open appendicectomy.

Methods: This was a historical cohort study of 245 400 patients who underwent open appendicectomy and population-based matched controls, identified by linkage of computer registries. Analyses were made with the life-table technique, Kaplan–Meier plots and Cox proportional hazards regression analysis.

Results: The cumulated risk of surgically treated small bowel obstruction after appendicectomy was 0·41 per cent after 4 weeks, 0·63 per cent after 1 year and 1·30 per cent after 30 years of follow-up, compared with 0·003 per cent at 1 year and 0·21 per cent after 30 years of follow-up among the non-operated controls. The highest risk was found after operation for other diagnoses (adjusted hazard ratio 5·2 (95 per cent confidence interval 4·6–5·8)), followed by operation for perforated appendicitis (adjusted hazard ratio 3·5 (3·1–3·8)), non-specific abdominal pain (adjusted hazard ratio 2·6 (2·3–3·0)) and mesenteric lymphadenitis (adjusted hazard ratio 2·4 (2·0–2·8)) compared with operation for non-perforated appendicitis. The relation with age was J shaped, with the lowest risk at 20–39 years. Women had a slightly lower risk than men.

Conclusion: The risk of postoperative small bowel obstruction needing surgical treatment after open appendicectomy is lower than previously thought. Perforated appendicitis, negative appendicectomy and high age are the risk factors.

Paper accepted 23 May 2001

British Journal of Surgery 2001, **88**, 1387–1391

Introduction

Postoperative small bowel obstruction is recognized as a common long-term adverse effect of appendicectomy but the frequency of this complication is not well known. The reported risk ranges from 0·2 to 10·7 per cent[1–7]. Most previous studies have been based on a small number of patients, with unclear definitions of patients and outcomes, incomplete follow-up and without taking account of the length of follow-up.

The aim of this study was to analyse the risk of postoperative small bowel obstruction needing surgical treatment in a cohort of patients subjected to open appendicectomy. The risk after appendicectomy was compared with that in a cohort of matched controls from the general population who had not been subjected to appendicectomy. The relation to the underlying diagnosis at operation, age at operation and sex was assessed.

Patients and methods

Study population

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in its Inpatient Register. Besides a national registration number (uniquely identifying every resident of Sweden), each record contains medical data, including surgical procedures performed (coded according to the Swedish Classification of Operation and Major Procedures) and diagnoses at discharge (coded through 1968 according to the International Classification of Diseases, 7th revision (ICD7), according to the 8th revision (ICD8) from 1969 to 1986 and according to the 9th revision (ICD9) thereafter). At the start in 1964 the register included only six counties, representing 20 per cent of the Swedish population, but more counties have been added successively, and the register has covered all Swedish hospitals since 1987.

Table 1 Characteristics of patients subjected to appendicectomy and matched controls, and main outcomes

	Appendicectomy	Controls
No. of patients	245 400	245 400
Age at appendicectomy (years)*	27·5(17·4)	27·5(17·4)
Women†	121 718 (50)	121 718 (50)
Length of follow-up (years)*	12·8(7·3)	13·0(7·2)
Total time at risk (years)	3 151 286	3 198 161
Patients operated for SBO		
During the index admission	741	0
At readmission during follow-up	1724	219
Total no. of patients operated for SBO	2465	219
Range of no. of readmissions	1–3	1–2
Total no. of operations for SBO	2659	236
Type of operation†		
Cutting of bands	841 (32)	58 (25)
Adhesiolysis	1467 (55)	125 (53)
Small bowel resection	351 (13)	53 (22)
Deaths within 30 days of operation for SBO	33	12
Deaths caused by SBO	18	7

*Values are mean(s.d.); †values in parentheses are percentages. SBO, small bowel obstruction

Since there is virtually no private hospital care in Sweden any study using the Inpatient Register is, in effect, population based.

Patients who underwent appendicectomy

All patients in the Inpatient Register who had a discharge diagnosis indicating that an appendicectomy had been performed between 1964 and 1993 were identified (*Table 1*). Patients undergoing incidental appendicectomy and those with an abdominal operation that preceded the appendicectomy were not included. Based on the discharge diagnosis the patients were divided into groups with perforated appendicitis, non-perforated appendicitis, non-specific abdominal pain, mesenteric lymphadenitis and other diagnoses. Other diagnoses included salpingitis, gastroenteritis, ovarian cysts, inflammatory bowel disease, diverticulitis, other diseases of the appendix and cholecystitis.

Control patients

For each eligible patient with a history of appendicectomy one control patient without a history of appendicectomy was matched according to age, sex and township of residence. To establish the place of residence for all patients at the time of surgery, data from the nationwide 1970, 1980 and 1990 censuses were used. Controls with an abdominal operation that preceded the appendicectomy in the matched case were excluded.

Follow-up

Patients who underwent appendicectomy and controls were linked to the Inpatient Register for 1964–1995. All patients who underwent appendicectomy and controls whose matched counterpart was missing after exclusion were also excluded, i.e. only complete pairs of patients who underwent appendicectomy and matched controls were kept for the analysis. Index admissions and all subsequent admissions with a discharge diagnosis of intestinal obstruction were identified. Patients with surgically treated small bowel obstruction were defined as all patients with a discharge diagnosis of intestinal obstruction combined with an operation code that indicated an abdominal operation for adhesions (adhesiolysis, division of peritoneal bands) or small bowel resection. Follow-up started on the day of discharge after the index operation of the matched case patient and ended on the date of the first readmission for surgically treated intestinal obstruction, the date of death or on 31 December 1995, whichever came first.

Statistical analysis

Differences in proportions were analysed with the χ^2 test. The risk of subsequent operation for small bowel obstruction after appendicectomy was analysed with the life-table method and Kaplan–Meier plots. The relation with the diagnosis at operation, age, sex and time period, and the difference in risk after appendicectomy compared with controls was analysed with Cox proportional hazards regression. The Stata computer program (Stata, College Station, Texas, USA) was used for the calculations and Kaplan–Meier plots (procedures *ltable*, *sts g* and *stcox*)[8]. Ninety-five per cent confidence intervals were used and $P < 0.05$ was regarded as significant.

Results

Some 245 400 pairs of patients and controls were followed up for a total of 6 349 447 person-years (*Table 1*). All patients had undergone open appendicectomy. During follow-up a total of 2465 patients had at least one operation for small bowel obstruction after appendicectomy (range 1–3 operations) and there was a total of 2659 operations. The corresponding figures for the controls were 219 primary operations and a total of 236 operations (range 1–2 operations). Bands were a more common cause of small bowel obstruction after appendicectomy than in controls (32 *versus* 25 per cent; $P = 0.025$). Thirty-three patients who

Table 2 Cumulated proportion of patients who underwent operation for small bowel obstruction at follow-up in relation to the diagnosis at the index operation

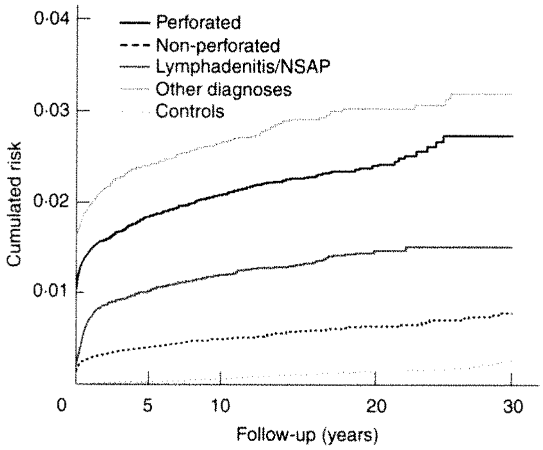
	Cumulated proportion with small bowel obstruction (%)			
Diagnosis	4 weeks	1 year	10 years	30 years
Appendicectomy	0·41 (0·38–0·44)	0·63 (0·60–0·66)	0·97 (0·93–1·01)	1·30 (1·23–1·36)
Perforated appendicitis	1·14 (1·03–1·26)	1·49 (1·36–1·63)	2·10 (1·95–2·27)	2·76 (2·48–3·08)
Non-perforated appendicitis	0·17 (0·15–0·19)	0·29 (0·27–0·32)	0·50 (0·47–0·54)	0·75 (0·68–0·82)
Lymphadenitis	0·16 (0·11–0·23)	0·70 (0·59–0·82)	1·14 (1·00–1·30)	1·42 (1·22–1·66)
Non-specific abdominal pain	0·32 (0·25–0·41)	0·77 (0·65–0·91)	1·30 (1·14–1·48)	1·72 (1·49–1·98)
Other diagnoses	1·68 (1·49–1·89)	1·99 (1·79–2·22)	2·67 (2·43–2·94)	3·24 (2·92–3·60)
Controls	0·00 (0·00–0·00)	0·00 (0·00–0·01)	0·06 (0·05–0·08)	0·21 (0·17–0·25)

Values in parentheses are 95 per cent confidence intervals. Proportions were calculated by life-table analysis

had appendicitis and 12 controls had died within 30 days of an operation for small bowel obstruction. The registered cause of death was small bowel obstruction in 18 of the patients who underwent appendicectomy and seven of the controls. The risk of death from small bowel obstruction was 2·6 times higher among patients who had been submitted to appendicectomy than among controls who had not. The risk of dying from small bowel obstruction after open appendicectomy can roughly be estimated to be 6 per million person-years.

The cumulated risk of surgically treated small bowel obstruction among patients who underwent appendicectomy was 0·41 per cent after 4 weeks of follow up, 0·63 per cent after 1 year, 0·97 per cent after 10 years and 1·30 per cent after 30 years, compared with 0·0004, 0·003, 0·06 and 0·21 per cent respectively among the controls (*Table 2*). Compared with the control population there was a 200-fold increased risk at 1 year after appendicectomy and a sixfold increased risk after 30 years.

The relation with diagnosis, age, time period at operation and sex was analysed with Cox proportional hazards regression within the operated group of patients. Compared with non-perforated appendicitis the highest risk of surgery for small bowel obstruction was found after appendicectomy for other diagnoses (adjusted hazard ratio 5·2 (95 per cent confidence interval 4·6–5·8)), followed by operation for perforated appendicitis (adjusted hazard ratio 3·5 (3·1–3·8)), non-specific abdominal pain (adjusted hazard ratio 2·6 (2·3–3·0)) and mesenteric lymphadenitis (adjusted hazard ratio 2·4 (2·0–2·8)). The cumulated risk in relation to the diagnosis in patients submitted to appendicectomy and in non-operated controls is presented as a Kaplan–Meier plot in *Fig. 1*.



No. at risk					
Perforated	32 201	25 407	16 177	4610	385
Non-perforated	158 539	134 562	94 496	29 888	2911
Lymphadenitis/NSAP	38 157	33 025	24 156	7498	617
Other diagnoses	16 503	13 663	9140	3415	412
Controls	245 400	209 586	146 306	46 737	4402

Fig. 1 Kaplan–Meier plots of the cumulated risk of surgically treated small bowel obstruction after open appendicectomy according to the diagnoses at operation and among matched controls. NSAP, non-specific abdominal pain

The relation with age was J shaped; the lowest risk after appendicectomy was at 20–39 years (adjusted hazard ratio 0·8 (0·7–0·9)), increasing to adjusted hazard ratio 2·0 (1·8–2·3) from age 70 years, compared with the risk for patients operated before the age of 20 years. Women had a slightly lower risk than men (adjusted hazard ratio 0·8 (0·8–0·9)).

Discussion

Surgically treated small bowel obstruction is only one part of a much larger problem of complications resulting from postoperative adhesions[9]. In this registry study it was impossible to delineate conservatively treated complications due to adhesions from other causes of abdominal pain. Surgically treated small bowel obstruction was therefore chosen as the hard endpoint of the study.

The absolute risk of small bowel obstruction after open appendicectomy was smaller than is usually expected. However, the risk was considerably increased relative to that of a control population of patients from the general population without a history of appendicectomy. Compared with the control population the risk was increased 200-fold at 1 year after appendicectomy, decreasing to sixfold at 30 years. The risk of dying from small bowel obstruction after open appendicectomy was estimated to be 6 per million person-years, or 2·6 times higher than that of controls who had not been submitted to appendicectomy.

The risk of postoperative small bowel obstruction subsequent to open appendicectomy was 0·41 per cent in the first 4 weeks and 0·63 per cent after 1 year. A slightly higher risk has been reported previously in smaller studies. Riber *et al.*[2] reported a frequency of intestinal obstruction of 0·33 per cent after 30 days and 0·79 per cent after 1 year of follow-up in 1544 patients, and Stewart *et al.*[7] reported a frequency of 0·65 per cent after 6 weeks in 1393 patients.

This study confirms the findings of others of a difference in risk in relation to the diagnosis at the index operation; there was a low risk after non-perforated appendicitis and a higher risk after operations for other diagnoses, perforated appendicitis, non-specific abdominal pain and mesenteric lymphadenitis. These results may have implications for the understanding of the pathogenesis of peritoneal adhesions. The cause of the increased risk after perforation is evident as peritonitis induces adhesions. When an uninflamed appendix is found at exploration of a patient with suspected appendicitis it is common practice to perform a wider exploration of the intestine and the pelvic organs. This wider exploration may cause more extensive damage to the peritoneal lining followed by an increased risk of adhesions and postoperative small bowel obstruction. This may explain the increased risk of small bowel obstruction after operations for other diagnoses, non-specific abdominal pain and mesenteric lymphadenitis. The eventual benefit from the wider exploration should therefore be weighed against the disadvantage of a more than doubled risk of postoperative intestinal obstruction.

However, there may be other explanations. It has recently been shown that patients with negative appendicectomies have an increased inflammatory response in the appendix as well as in the peripheral blood[10,11]. An increased inflammatory response has also been shown among patients who are prone to develop peritoneal adhesions[12]. This suggests that an inflammatory response may be a common aetiological factor, both for the pain that led to the negative exploration and to the peritoneal adhesions. The increased risk of small bowel obstruction after negative appendicectomy may therefore be attributed to patient-related factors and not only to the surgical technique.

The results in this large cohort study may have a bearing on the current controversy regarding the use of laparoscopy in the management of patients with suspected appendicitis. Laparoscopic operations are assumed to induce fewer peritoneal adhesions and to have a lower risk of subsequent small bowel obstruction[13]. However, there is currently limited evidence in support of this assumption and no evidence has been presented that shows any clinical benefit of the reduction in peritoneal adhesions. Laparoscopy also introduces other mechanisms for small bowel obstruction, such as incarceration at the trocar sites[14]. One study reported a risk of early postoperative small bowel obstruction after laparoscopic appendicectomy of 0·17 per cent[14]. This figure is identical to that found in the present study after open appendicectomy for non-perforated appendicitis. The assumption of the superiority of laparoscopic appendicectomy in this regard may therefore be questioned.

Acknowledgements

This study was supported by grants from the Health Research Council in the Southeast of Sweden and the Committee for Research and Development, Jönköping County Council.

References

1 Ahlberg G, Bergdahl S, Rutqvist J, Soderquist C, Frenckner B. Mechanical small-bowel obstruction after conventional appendectomy in children. *Eur J Pediatr Surg* 1997; **7:** 13–15.

2 Riber C, Soe K, Jorgensen T, Tonnesen H. Intestinal obstruction after appendectomy. *Scand J Gastroenterol* 1997; **32:** 1125–8.

3 Zbar RI, Crede WB, McKhann CF, Jekel JF. The postoperative incidence of small bowel obstruction following standard, open appendectomy and cholecystectomy: a six-year retrospective cohort study at Yale-New Haven Hospital. *Conn Med* 1993; **57:** 123–7.

4 Arnbjornsson E. Small intestinal obstruction after appendectomy: an avoidable complication? *Curr Surg* 1984; **41:** 354–7.

5 Hansen JH. Adhaerenceileus. Forekomst efter forskellige laparotomityper. *Ugeskr Laeger* 1982; **144:** 2919–21.

6 Sykes PA, Schofield PF. Early postoperative small bowel obstruction. *Br J Surg* 1974; **61:** 594–600.

7 Stewart RM, Page CP, Brender J, Schwesinger W, Eisenhut D. The incidence and risk of early postoperative small bowel obstruction. A cohort study. *Am J Surg* 1987; **154:** 643–7.

8 Stata Corporation. *Stata Statistical Software: Release 6.0* College Station, Texas: Stata Corporation, 1999.

9 Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D *et al* Adhesion-related hospital readmissions after abdominal and pelvic surgery· a retrospective cohort study. *Lancet* 1999; **353**: 1476–80.

10 Wang Y, Reen DJ, Puri P. Is a histologically normal appendix following emergency appendicectomy always normal? *Lancet* 1996; **347**: 1076–9.

11 Chia YW, Carachi R, Armstrong AA, McGarry GW, Carrington D Serum alpha interferon in children with right iliac fossa pain. *J R Soc Med* 1993, **86**: 259–60.

12 Saba AA, Godziachvili V, Mavani AK, Silva YJ. Serum levels of interleukin 1 and tumor necrosis factor alpha correlate with peritoneal adhesion grades in humans after major abdominal surgery. *Am Surg* 1998; **64**: 734–6.

13 de Wilde RL. Goodbye to late bowel obstruction after appendicectomy. *Lancet* 1991; **338**: 1012(Letter).

14 Duron JJ, Hay JM, Msika S, Gaschard D, Domergue J, Gainant A *et al*. Prevalence and mechanisms of small intestinal obstruction following laparoscopic abdominal surgery: a retrospective multicenter study. French Association for Surgical Research. *Arch Surg* 2000; **135**: 208–12.

Original article

Strategy for the surgical management of patients with idiopathic megarectum and megacolon

C. B. Ó Súilleabháin, J. H. Anderson, R. F. McKee and I. G. Finlay

Department of Coloproctology, Royal Infirmary, Glasgow G32 2ER, UK
Correspondence to: Mr I. G. Finlay (e-mail: i.g.finlay@colorectal.demon.co.uk)

Background: Several surgical procedures have been used to treat idiopathic megabowel. A structured approach to the surgical management of megarectum/colon is reported.

Methods: Twenty-eight consecutive patients with megabowel referred for surgery were reviewed. All patients had conservative treatment for 6 months. Those failing to improve underwent full-thickness biopsy of the anorectal junction, anorectal physiology studies, colonic transit studies and evacuation proctography. Surgery involved excision of the abnormal large bowel and formation of an anastomosis (coloanal or ileoanal) using 'normal' bowel identified either by a defunctioning stoma or colonic motility studies.

Results: Eight patients responded to conservative management. Two patients were lost to follow-up and one died from unrelated causes. Two of the 17 patients who underwent full-thickness biopsy were cured by the procedure. Anorectal physiology, colonic transit and evacuation studies did not aid selection of the surgical procedure performed in 15 patients: proctectomy and coloanal anastomosis (six), restorative proctocolectomy (three), panproctocolectomy (one) and defunctioning stoma (five). At a median follow-up of 3·6 years, 13 of 15 evaluable patients had a satisfactory outcome.

Conclusion: Approximately 40 per cent of patients with megabowel referred for surgery responded to conservative treatment. The remaining patients may be treated successfully by surgery. The use of either a 'diagnostic' defunctioning stoma or colonic motility studies may aid in the choice of surgical procedure.

Presented to the American College of Colon and Rectal Surgeons 100th Anniversary and Tripartite Meeting, Washington DC, USA, May 1999
Paper accepted 1 June 2001

British Journal of Surgery 2001, **88**, 1392–1396

Introduction

Megabowel is an uncommon clinical condition that presents as intractable constipation in childhood or adolescence[1,2]. It includes megarectum, megasigmoid, megacolon or a combination of these[3]. Although causes include Hirschprung's disease, Chagas' disease and chronic intestinal pseudo-obstruction[4], at least 50 per cent of cases are idiopathic[5,6], and an intact anorectal inhibitory reflex and ganglia are found on full-thickness rectal biopsy. Consequently, there is no recognized diagnostic test for idiopathic megarectum/colon other than evidence of increased rectal or colonic diameter on radiological examination.

Patients with idiopathic megarectum/colon are managed medically in the first instance using laxatives and enemas but surgery may be indicated if conservative management fails. Although several surgical procedures, including restorative proctocolectomy, proctectomy with coloanal anastomosis and segmental colonic resection, have been used, there are no criteria for selecting a particular operation for an individual patient.

A structured approach to the surgical management of megarectum/colon, using clinical criteria and investigations including colonic motility studies, is reported.

Patients and methods

Twenty-eight consecutive patients (19 males) with megarectum/colon referred to a specialist colorectal unit between 1988 and 1997 were studied. The median age was 21 (range 4–71) years. The median duration of symptoms at the time of presentation was 12·6 (range 1–40) years. The principal presenting symptom was either chronic constipation (16 patients) or faecal incontinence (12).

At presentation, three patients had already had a colostomy (one after Hartmann's resection and two for acute large bowel obstruction). A further five patients had undergone lower gastrointestinal surgery (segmental resection for volvulus (two), reconstruction of an imperforate anus (two) and Soave procedure (one)).

The diagnosis of megarectum/colon was made on barium enema in 26 patients, at surgery in one patient and on proctography in one patient. All 28 patients had megarectum; five patients also had megasigmoid while ten had megarectum, megasigmoid and megacolon.

Clinical management

Clinical history and physical examination noted in particular the duration of symptoms and the presence or absence of a patulous anal sphincter. The severity of symptoms and the desire for further investigation and treatment varied between patients. In the first instance all patients were given a trial of conservative management for a period of 6 months comprising the use of laxatives and enemas. Only those who failed to respond and continued to have severe symptoms were considered for surgery.

All patients for whom surgery was considered underwent anorectal physiology studies to measure the anorectal inhibitory reflex and anal canal pressures (resting and squeeze). Evacuation proctography and a standard 20-marker colonic transit study were performed before full-thickness biopsy of the anorectal junction under general anaesthesia.

The surgical approach changed during the study. Initially a loop stoma was fashioned above the dilated segment of bowel to determine whether the proximal bowel functioned normally and whether patients were asymptomatic with the stoma *in situ*.

When a research technique to measure colonic motility became available in the department, it was used in an attempt to distinguish normal from abnormal colon (in the final seven patients). The technique, which has been described previously[7], comprised the insertion of a 190-cm multilumen catheter (M^3 eight-lumen colonic catheter; Arndorfer, Greendale, Wisconsin, USA) into the proximal colon using a colonoscope. Sterile water was perfused through each channel at a rate of 0·6 ml/min and pressure was recorded from each port for 24 h. Motility indices were measured from a computer recording for 1 h before and after a standardized 1000-kcal meal stimulus and after a subcutaneous neostigmine (0·01 mg/kg) stimulus. In addition the total numbers of high-amplitude contractions were counted during the 24-h observation period.

Statistical analysis

Results are expressed as median (range) or mean(s.d.). The anorectal physiology results were compared with age- and gender-matched controls from this department using a Mann–Whitney *U* test. $P < 0·05$ was considered significant.

Results

Eight of the 28 patients responded to 6 months of conservative management and were discharged from follow-up. Six of these patients had only a megarectum. A further two patients failed to attend for review and were lost to follow-up. One patient died from an unrelated cause during the review period. The remaining 17 patients, who remained symptomatic, underwent anorectal physiology and examination under anaesthesia with full-thickness rectal biopsy.

The mean(s.d.) resting anal canal pressure was lower in patients than in controls (45(22) and 72(38) mmHg respectively; $P < 0·04$). There was no significant difference between the groups in mean squeeze pressure (100(21) and 113(45) mmHg; $P = 0·68$). Two of the 17 patients had complete resolution of their symptoms after full-thickness rectal biopsy; both had ganglia in the myenteric plexus.

Colonic motility studies were performed in seven patients. Three patients had evidence of high-amplitude propagated contractions in the proximal colon with a normal response to neostigmine, and were therefore treated by proctectomy and coloanal anastomosis. In the remaining four patients the colon failed to respond to neostigmine and no high-amplitude contractions were identified; these patients had an ileal pouch.

Fifteen patients had surgery. Although none was able to empty on evacuation proctography, seven had evidence of an intact anoinhibitory reflex on testing. The surgical procedures performed were proctectomy and coloanal anastomosis (six), restorative proctectomy (three), panproctocolectomy (one) and defunctioning stoma (five). The median follow-up after surgery was 3·6 (range 1–5·5) years.

Proctectomy and coloanal anastomosis

Proctectomy and coloanal anastomosis was performed in six patients; all had either a megarectum alone or with a limited megasigmoid. A normal functioning proximal colon was identified by colonic physiology studies in three patients and by defunctioning stoma in three patients. Four of these six patients have had an excellent result, and no longer use enemas or laxatives. One patient continues to complain of urgency and occasional incontinence. One patient subsequently developed ulcerative colitis and required a colectomy and end-ileostomy, and is now awaiting ileal pouch reconstruction.

Restorative proctocolectomy or panproctocolectomy

Four patients were offered a restorative proctocolectomy. Three had a megacolon in addition to a megarectum. All had undergone colonic physiology studies, which showed an absence of mass colonic contractions in the proximal colon and failure to respond to neostigmine stimulation. Colonic transit studies were prolonged in all four patients. In one of these patients, who had Marfan's syndrome, the procedure was abandoned because of insufficient mesenteric length and a permanent ileostomy was fashioned. The remaining three patients have satisfactory pouch function, although one has had intermittent pouchitis.

Defunctioning stoma

In five patients a temporary ileostomy was performed. Two patients have elected to keep the ileostomy and undergo no further surgery because of resolution of their symptoms. Two patients await physiological studies; the choice of surgical procedure will be based on these results. One patient underwent an emergency loop sigmoid colostomy. The colostomy was closed at the patient's request and no further surgery has been performed. This patient has defaulted further follow-up.

Discussion

Idiopathic megarectum/colon is an unusual and poorly understood clinical condition. Consequently, as in the present study, many patients are treated conservatively[1]. The response to treatment is dependent upon the extent of disease; patients with megarectum alone do better than those with megacolon[8].

Surgical intervention was necessary in 17 of the 28 patients in the present study. Before operation they all had a full-thickness biopsy of the anorectal junction to exclude ultrashort Hirschprung's disease. Two patients had resolution of their symptoms despite the fact that ganglion cells were observed in all of the histological specimens. Given that these biopsies were 'diagnostic' rather than therapeutic this was an unexpected outcome. Perhaps an 'ultra-ultrashort' segment of Hirschsprung's disease was missed on biopsy.

Although anorectal manometry was used in this study it did not help in either the selection of patients for surgery or in the choice of surgical procedure. Anal canal resting pressures were invariably low and the anorectal inhibitory reflex was frequently absent. However, the finding of ganglion cells on histological examination suggests that this may be due to failure of the intrarectal balloon to stretch the dilated rectal wall rather than to loss of the reflex. Similarly, none of the patients who underwent surgery were able to expel a balloon before operation but this did not influence outcome.

Many surgical procedures have been used in the treatment of megarectum/colon including colectomy and ileorectal/ileosigmoid anastomosis[6,9,10], proctectomy and coloanal anastomosis[10], pull-through procedures[10], Duhamel operation[11], anal myomectomy[12] and, more recently, restorative proctocolectomy[3,13,14]. The outcome after these procedures is variable, with poor function leading to a high reoperation rate for continuing severe constipation[8,9,15–17]. This variation in surgical approach probably occurs because the pathophysiology of megabowel is poorly understood. In particular it is unknown whether the abnormality is limited to the dilated bowel or also involves non-dilated gut. Although clinical experience has shown that a stoma fashioned above a dilated segment of bowel functions well while a stoma utilizing dilated bowel usually fails[2], there are several reports of recurrence of megacolon after surgical resection of the entire macroscopically dilated bowel[9,17,18].

In the early part of the present study a stoma was fashioned above the dilated bowel in order to identify 'normal gut' which could be used for an anastomosis. This technique was also used to determine whether with a period of 'rest' the diameter of the distal megabowel might reduce, thereby improving rectal sensation. No improvement occurred in bowel diameter despite the presence of a stoma, in some cases for several years. In the absence of more sophisticated tests, however, the use of a defunctioning stoma in this way may help in selecting patients for either proctectomy and coloanal anastomosis or restorative proctocolectomy.

There is increasing interest in the use of restorative proctectomy for both megarectum and megacolon, with a reported success rate as high as 85 per cent[19]. The largest series to date comprised only 14 patients with a success rate of 70 per cent[3]. Although there was concern that the low anal sphincter pressures would lead to incontinence if a pouch was used this has not occurred in either the present or previous studies[14]. An alternative surgical approach involves resection of the dilated bowel with formation of a coloanal anastomosis[16,17]. This has the advantage of retaining a length of proximal colon and should give superior functional results to those achieved by an ileal pouch. Success rates of up to 75 per cent have been reported[16,17] but reoperation was necessary for recurrent megacolon in many patients, suggesting that a more extensive colonic abnormality exists in some patients. The optimum procedure therefore (proctectomy and coloanal anastomosis or restorative proctocolectomy) has not been established.

In the later stage of the present study colonic physiology was used in an attempt to develop a more objective method of identifying normal proximal colon. This is a research technique that is recognized to have substantial limitations but has been used to study colonic motility in postchildbirth constipation[20,21], and to identify colonic neuropathy in patients with rectal prolapse[7]. Although the numbers in the present study are too small to draw firm conclusions, this technique may have a future role in selecting the type of operation for patients with megabowel.

In conclusion, almost half of all patients with megabowel will respond to either conservative measures or full-thickness biopsy of the anorectal junction. A suggested algorithm for those who require surgery is given in *Fig. 1.* The principal options are restorative proctocolectomy or proctectomy and coloanal anastomosis. In the absence of sophisticated tests these data suggest that patients with megacolon should probably be offered a pouch procedure while those with only megarectum may be considered for proctectomy and coloanal anastomosis if a preliminary defunctioning colostomy works well. The development of techniques for the measurement of colonic motility may allow the identification of patients with megarectum who also have a proximal abnormality and therefore require an ileal pouch.

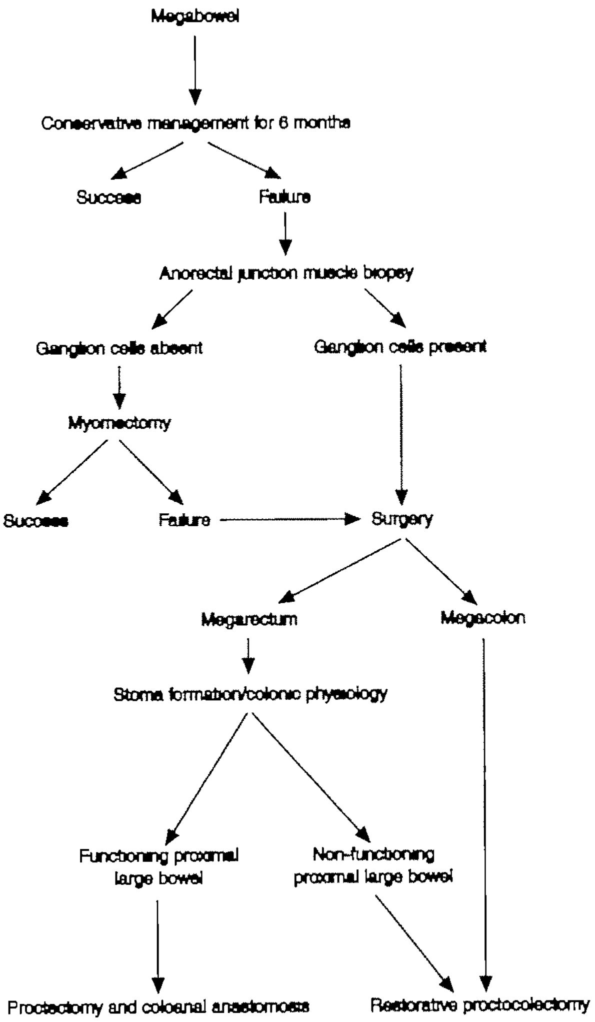

Megabowel
Conservative management for 6 months
Success
Failure
Anorectal junction muscle biopsy
Ganglion cells absent
Ganglion cells present
Myomectomy
Success
Failure
Surgery
Megarectum
Megacolon
Stoma formation/colonic physiology
Functioning proximal large bowel
Non-functioning proximal large bowel
Proctectomy and coloanal anastomosis
Restorative proctocolectomy

Fig. 1 Strategy for the surgical management of megabowel

References

1 Gattuso JM, Kamm MA. Review article: the management of constipation in adults. *Aliment Pharmacol Ther* 1993, **7:** 487–500.

2 Gattuso JM, Kamm MA, Morris G, Britton KE. Gastrointestinal transit in patients with idiopathic megarectum. *Dis Colon Rectum* 1996; **39:** 1044–50.

3 Pfeifer J, Agachan F, Wexner SD. Surgery for constipation: a review. *Dis Colon Rectum* 1996; **39:** 444–60.

4 Todd IP. Discussion on megacolon and megarectum with the emphasis on conditions other than Hirschsprung's disease. *Proc R Soc Med* 1961; **54:** 1035–40.

5 Preston DM, Hawley PR, Lennard-Jones JE, Todd IP. Results of colectomy for severe idiopathic constipation in women (Arbuthnot Lane's disease). *Br J Surg* 1984; **71:** 547–52.

6 Lane RH, Todd IP. Idiopathic megacolon· a review of 42 cases. *Br J Surg* 1977; **64:** 307–10.

7 Brown AJ, Horgan AF, Anderson JH, McKee RF, Finlay IG. Colonic motility is abnormal before surgery for rectal prolapse. *Br J Surg* 1999; **86:** 263–6.

8 Keighley MR. Megacolon and megarectum. In: Keighley MR, Williams NS, eds *Surgery of the Anus, Rectum and Colon*. Vol 1. London: WB Saunders, 1993: 658–73.

9 Belliveau P, Goldberg SM, Rothenberger DA, Nivatvongs S. Idiopathic acquired megacolon: the value of a subtotal colectomy *Dis Colon Rectum* 1982; **25:** 118–21.

10 McCready RA, Beart RW. The surgical treatment of incapacitating constipation associated with idiopathic megacolon. *Mayo Clin Proc* 1979; **54:** 779–83.

11 Stabile G, Kamm MA, Hawley PR, Lennard-Jones JE. Results of the Duhamel operation in the treatment of idiopathic megarectum and megacolon. *Br J Surg* 1991; **78:** 661–3.

12 Hata Y, Sasaki F, Uchino J. Sphincteromyectomy and sphincteroplasty in chronic constipation with megarectum. *J Pediatr Surg* 1988; **23:** 141–2.

13 Vernava AM III, Robbins PL, Brabbee GW. Restorative resection: coloanal anastomosis for benign and malignant disease. *Dis Colon Rectum* 1989; **32:** 690–3.

14 Brown SR, Shorthouse AJ. Restorative proctocolectomy for idiopathic megarectum. postoperative recovery of hypotonic anal sphincters. Report of two cases. *Dis Colon Rectum* 1997, **40:** 625–7.

15 Stabile G, Kamm MA, Hawley PR, Lennard-Jones JE. Colectomy for idiopathic megarectum and megacolon. *Gut* 1991; **32:** 1538–40.
16 Stabile G, Kamm MA, Phillips RK, Hawley PR, Lennard-Jones JE. Partial colectomy and coloanal anastomosis for idiopathic megarectum and megacolon. *Dis Colon Rectum* 1992; **35:** 158–62.
17 Stewart J, Kumar D, Keighley MR. Results of anal or low rectal anastomosis and pouch reconstruction for megarectum and megacolon. *Br J Surg* 1994; **81:** 1051–3.
18 Stabile G, Kamm MA, Hawley PR, Lennard-Jones JE. Results of stoma formation for idiopathic megarectum and megacolon. *Int J Colorectal Dis* 1992; **7:** 82–4.
19 Hosie KB, Kmiot WA, Keighley MR. Constipation: another indication for restorative proctocolectomy. *Br J Surg* 1990; **77:** 801–2.
20 Di Lorenzo C, Flores AF, Reddy SN, Hyman PE. Use of colonic manometry to differentiate causes of intractable constipation in children. *J Pediatr* 1992; **120:** 690–5.
21 MacDonald A, Carter K, Baxter JN, Wright R, Finlay IG. Mass inaction: the hallmark of constipation after childbirth or hysterectomy. *Br J Surg* 1994; **81:** 750(Abstract).

Original article

Hospital caseload and the results achieved in patients with rectal cancer

F. Marusch, A. Koch, U. Schmidt, M. Pross, I. Gastinger and H. Lippert

Institute for Quality Management in Operative Medicine at the Otto-von-Guericke University, Magdeburg, Germany
Correspondence to: Dr F. Marusch, Department of Surgery, Otto-von-Guericke-University, Leipziger Strasse 44, D-39120 Magdeburg, Germany
(e-mail: marusch-cottbus@t-online.de)

Background: The aim of the study was to investigate the impact of hospital caseload on the short-term postoperative outcome of patients with rectal carcinoma.

Methods: A multicentre study involving 75 German hospitals was carried out between January and December 1999. Some 1463 patients with rectal carcinoma were studied.

Results: The hospitals were divided into three groups by annual caseload as follows: less than 20 (group 1), 20–40 (group 2) and more than 40 (group 3). The groups were identical in terms of age, gender, height, weight, tumour stage, risk factors and American Society of Anesthesiologists classification. Postoperative morbidity was less in hospitals with a case volume of more than 20 patients per year (41·7 per cent in group 2 *versus* 49·9 per cent in group 1). The proportion of patients undergoing abdominoperineal resection with a permanent stoma was less in hospitals with a case volume of more than 40 patients per year (26·4 per cent in group 3 *versus* 34·0 per cent in group 2).

Conclusion: A large caseload in rectal surgery results in a significant reduction in permanent stoma formation and postoperative morbidity.

Paper accepted 23 May 2001

British Journal of Surgery 2001, 88, 1397–1402

Introduction

Numerous studies have demonstrated a relationship between hospital surgical volume and both short- and long-term results of complex gastrointestinal and other forms of surgery for carcinoma[1–4]. In the surgical treatment of pancreatic cancer (Whipple's procedure)[5–10], thyroidectomy[11,12], resection of the liver[13,14], mastectomy or lumpectomy for breast cancer[15] and prostatectomy[16,17], the hospital volume has a decisive impact on morbidity and mortality rates, and long-term patient survival. The present study was undertaken to establish whether experience in rectal carcinoma impacts on short-term postoperative outcome.

Patients and methods

This was a prospective multicentre observational study. The data evaluated were obtained in the calendar year 1999. Seventy-five German hospitals of all sizes (from small local hospitals to large university hospitals) participated, on a purely voluntary basis, and no hospital was excluded. All surgical departments in the five German states of Brandenburg, Saxony, Saxony-Anhalt, Thuringia, Mecklenburg-West Pomerania were invited to participate. The total number of patients with a colorectal carcinoma involved was 3756. These five states have a population of some 15 million, and about 7000 new colorectal carcinomas per year may be expected. Patients included in the study may be assumed to be representative for the region as a whole, and any selection bias therefore small. This region of Germany has 219 hospitals, of which 150 carry out colorectal surgery, so 50 per cent of all relevant hospital departments participated.

Every patient with a colorectal carcinoma who presented within the study period was admitted. The data obtained from a total of 3756 patients were entered into a special standardized questionnaire that contained 68 fields covering the preoperative findings, type of operation, postoperative course and tumour histology. The patients continue to be followed up annually. The questionnaires were completed by the senior registrar of each hospital/department. To ensure accuracy, all participating surgeons attended three weekend study information sessions.

Since the study was designed as an observational study, approval by an ethics committee was not required. All patients allowed their data to be recorded. These data were checked for correctness and completeness by the study director, who conducted a number of random checks in each department during the period of the study to compare the entries in the questionnaire with the data in the patients' hospital records. These checks revealed no discrepancies in the reported data. Any implausible or incomplete questionnaires were checked in the same manner. Further, the patient data from each department were investigated for completeness (all patients included) by comparing computer records of patients undergoing surgery for colorectal cancer. The data were analysed using the SPSS 9.0 statistical program (SPSS, Chicago, Illinois, USA).

To investigate the influence of experience on the results of rectal surgery, the hospitals were divided into those with fewer than 20 patients (group 1: 44 hospitals, $n = 444$, mean 10 (range 5–19) patients), those with 20–40 (group 2: 22 hospitals, $n = 544$, mean 25 (range 20–33) patients) and those with more than 40 patients (group 3: nine hospitals, $n = 475$, mean 53 (range 44–67) patients). The experience of individual surgeons was not considered.

All statistical evaluations were carried out in an explorative sense, taking $P < 0{\cdot}05$ to be significant. Two-dimensional frequency distributions were compared using the χ^2 test. During this procedure, neighbouring categories were considered together wherever necessary. Continuous variables, such as age and time (e.g. postoperative stay), were evaluated with the Welch test or, in the event of more than two groups, with a one-way analysis of variance. Additional Tukey multiple comparisons were also employed. For very large samples, statistical significance may not be of clinical relevance.

A cut-point search was conducted to determine the number of patients needed to best differentiate between hospitals with a high and low morbidity or abdominoperineal resection (APR) rate. This search was done in steps of two patients per hospital. A χ^2 test was used to evaluate the number of cases.

Results

Some 3756 patients with a carcinoma of the colon or rectum were admitted to the study. These patients were treated in a total of 75 hospitals/institutions in five German states, and accounted for about 54 per cent of all new colorectal carcinomas in the region.

Among the patients, 1463 had a carcinoma of the rectum and are the subject of this study. Rectal carcinomas were defined as tumours whose proximal extent was not more than 16 cm distant from the anal verge. A total of 1431 patients underwent surgery (97·8 per cent), with resection of the tumour in 1287 (resection rate 89·9 per cent). Some 1079 patients (83·8 per cent) were resected for cure (i.e. histologically clear margins) and 208 (16·2 per cent) for palliation.

The three hospital groups did not differ in terms of the ratio of male to female patients, age, body mass index, individual risk factors, American Association of Anesthesiologists (ASA) classification, stage distribution (Union Internacional Contra la Cancrum), or resection rates for the different tumour locations (less than 4 cm, 4 to less than 8 cm, 8 to less than 12 cm, 12–16 cm). Total mesorectal excision (TME) was performed in 58·6 per cent of operations in group 1 hospitals (232 of 397), 61·5 per cent (289 of 469) in group 2 and 61·8 per cent (260 of 421) in group 3 (*P* not significant). APR rates according to distance of the tumour from the anal verge and hospital group are given in *Table 1*.

A stapled anastomosis was performed in 86·9 per cent of cases (661 of 761): 88·0 per cent (219 of 249) in group 1 hospitals, 90·7 per cent (234 of 258) in group 2 and 81·9 per cent (208 of 254) in group 3. In group 3 hospitals significantly more anastomoses were hand-sewn ($P = 0{\cdot}01$).

Intraoperative complications occurred during 142 (9·9 per cent) of 1431 procedures. These included iatrogenic perforation of the tumour, haemorrhage (intraoperative blood replacement of more than 2 units of red blood cells), ureteric or urethral injury, injuries to the bladder, spleen,

Table 1 Abdominoperineal resection rates as a function of the distance of the tumour from the anal verge

	Group 1		Group 2		Group 3		
Site of tumour*	Resections†	APR (%)	Resections†	APR (%)	Resections†	APR (%)	*P*
< 4 cm	52	86·5	83	90·4	62	90·3	n.s.
4 to < 8 cm	117	50·4	122	56·6	127	39·4	0·023
8 to < 12 cm	122	12·4	153	9·8	146	3·4	0·023
12 to 16 cm	106	0	111	0	86	0	–
All sites	397	29·8	469	34·0	421	26·4	0·044

*Distance of the tumour from the anal verge. †Total number of resections (with or without anastomosis). APR, abdominoperineal resection; n.s., not significant. χ^2 test

Table 2 Intraoperative complications

	No. of intraoperative complications			
Site of tumour*	Group 1	Group 2	Group 3	*P*
< 4 cm	9 (14·1)	6 (6·6)	4 (5·7)	n.s.
4 to <8 cm	30 (22·7)	13 (9·0)	16 (11·5)	0·003
8 to < 12 cm	15 (11·5)	16 (9·3)	14 (8·9)	n.s.
12–16 cm	6 (5·2)	8 (6·3)	5 (5·6)	n.s.
All sites	60 (13·6)	43 (8·1)	39 (8·5)	0·008

Values in parentheses are percentages. *Distance of the tumour from the anal verge. n.s., Not significant. χ^2 test

Table 3 General postoperative complications

	No. of general complications			
Site of tumour*	Group 1	Group 2	Group 3	*P*
< 4 cm	18 (28·1)	27 (29·7)	15 (21·4)	n.s.
4 to <8 cm	40 (30·3)	44 (30·6)	40 (28·8)	n.s.
8 to < 12 cm	39 (30·0)	45 (26·2)	36 (22·8)	n.s.
12–16 cm	35 (30·4)	36 (28·6)	22 (24·4)	n.s.
Total	132 (29·9)	152 (28·5)	113 (24·7)	n.s.

Values in parentheses are percentages. *Distance of the tumour from the anal verge. n.s., Not significant. χ^2 test

Table 4 Specific postoperative complications

	No. of specific postoperative complications			
Site of tumour*	Group 1	Group 2	Group 3	*P*
< 4 cm	22 (34·4)	28 (30·8)	25 (35·7)	n.s.
4 to <8 cm	50 (37·9)	38 (26·4)	45 (32·4)	n.s.
8 to <12 cm	42 (32·3)	43 (25·0)	38 (24·1)	n.s.
12–16 cm	38 (33·0)	23 (18·3)	28 (31·1)	0·02
Total	152 (34·5)	132 (24·8)	136 (29·8)	0·004

Values in parentheses are percentages. *Distance of the tumour from the anal verge. n.s., Not significant. χ^2 test

small bowel and neighbouring organs, or complications associated with pneumoperitoneum (*Table 2*). The general postoperative complication rate was 27·7 per cent (*Table 3*) and the overall rate of specific postoperative complications was 29.4 per cent (*Table 4*).

Comparison between group 2 and 3 hospitals in terms of specific complications revealed no significant differences. In contrast, the difference between group 1 hospitals and those in groups 2 and 3 was significant (*P* = 0·005). There was no difference between hospital groups in terms of complications that required reoperation (afterbleeds, burst abdomen, ileus, anastomotic leakage): 12·0 per cent (53 of 441) in group 1, 7·7 per cent (41 of 533) in group 2 and 9·4 per cent (43 of 457) in group 3 (*Table 5*).

Table 5 Anastomotic leak rate following resection of the rectum

Anastomotic leak	Group 1 (*n* = 249)	Group 2 (*n* = 258)	Group 3 (*n* = 254)	*P*
Requiring reoperation	15 (6·0)	7 (2·7)	18 (7·1)	n.s.
Not requiring reoperation	13 (5·2)	5 (1·9)	15 (5·9)	n.s.
All leaks	28 (11·2)	12 (4·7)	33 (13·0)	0·003

Values in parentheses are percentages. n.s., Not significant. χ^2 test

The postoperative morbidity rate was 44·2 per cent (633 of 1431). It was lower in groups 2 and 3 than in group 1: 49·9 per cent (220 of 441) in group 1, 41·7 per cent (222 of 533) in group 2 and 41·8 per cent (191 of 457) in group 3 (*P* = 0·016). The overall hospital mortality rate was 5·2 per cent (*n* = 76). There was no difference between groups. The mean postoperative hospital stay was significantly shorter in groups 2 and 3 than in group 1: 21·3 (median 18 (range 1–102)) days in group 1, 18·0 (median 16 (range 0–70)) days in group 2 and 18·3 (median 15 (range 2–106)) days in group 3 (*P* = 0·001).

The cut-point search showed the best differentiation between hospitals with high and low morbidity rates for a caseload of 20 patients per year. Hospitals with a caseload of less than 20 patients per year had a morbidity rate of 51·7 per cent compared with 40·0 per cent for those with more than 20 patients. For the APR rate, the cut-point search identified a clear differentiation between hospitals for a caseload of 32 patients per year. Hospitals with more patients had an extirpation rate of 26·5 per cent, compared with 32·6 per cent for those with a smaller caseload.

Discussion

Variations have been reported in the outcome of patients undergoing surgery for rectal carcinoma between various centres and individual surgeons[18]. However, the prognostic significance of the surgeon-related factor is uncertain. Individual studies have reported a surgeon-related difference in the results of resection for colorectal carcinoma[18–25]. More recently, the prognostic significance of the hospital or the advantage of a high-volume hospital in terms of morbidity, mortality and patient outcome has been discussed[19,26–32]. In the present study, the individual surgeon was not considered, since differences in the organization and administration of staff in surgical institutions in the German-speaking countries make it possible to report only on the institutional results, which fall within the responsibility of the head of department.

Simons *et al.*[24] reported that hospital environment and experience (surgical caseload) appear to impact significantly on outcome, and showed that hospitals with a significantly higher caseload achieved significantly better survival rates. Harmon *et al.*[33] defined hospital volume as follows: low (less than 40), medium (40–70) and high (more than 70) cases per year (colonic and rectal carcinomas were considered together). They showed that surgeons with a medium volume achieved an excellent outcome (similar to that achieved by high-volume surgeons) when they operated in hospitals with a medium or high volume, but not when they worked in low-volume hospitals[33]. Blomqvist *et al.*[34] reported that the 1-year relative survival rate among patients with rectal cancer residing in the catchment area of a large regional hospital was 76 per cent compared with 72 per cent for small local hospitals. However, studies carried out by Parry *et al.*[35] on 927 patients with primary colorectal carcinoma in England did not support an association between volume of work and patient outcome. Simunovic *et al.*[36] concluded that centralizing treatment for rectal carcinoma in high-volume or teaching hospitals would probably not lead to an improvement in surgical quality. In contrast, other authors call for just such a centralization and specialization in appropriate centres[18]. In the present study, the three groups of hospitals were comparable with regard to the distribution of risk factors, ASA classification and tumour stage. The benefit associated with hospitals with most experience in rectal surgery (group 3) was seen in the rate of APR. Hospitals in groups 1 and 2 made more frequent use of stapled anastomosis than those in group 3. Although an analysis by McRae and McLeod[37] indicated equality of stapled and hand-sewn anastomoses, the latter nevertheless have certain advantages with regard to intraoperative technical problems and postoperative stenosis rates. However, whether an advantage for group 3 hospitals can be concluded from this is doubtful. The overall anastomotic leak rate, including leaks both requiring operative treatment and those not requiring such treatment, was significantly lower in group 2. This can be explained by the significantly higher APR rate in group 2 *versus* group 3 for tumours located between 4 and 12 cm from the anal verge. For lesions below 8 cm, the risk of anastomotic insufficiency is appreciably higher. Overall, the anastomotic leak rate in this study was 9·6 per cent for rectal carcinoma. The incidence of clinically manifest anastomotic insufficiency after rectal resection is reported to lie between 3 and 30 per cent[25,38,39]. The rate appears to correlate directly with distance from the anal verge. Carlsen *et al.*[40] described an increase in anastomotic leakage following introduction of TME, a finding that decreased with increasing experience in the technique. The TME rate did not differ between the hospital groups in this study, so differences in postoperative results cannot be related to TME.

Overall, the morbidity rate in groups 2 and 3 was significantly lower than that in group 1. Postoperative hospital stay was significantly shorter in groups 2 and 3. In comparison to North American hospitals, however, hospital stay in general was longer, owing to differences in the healthcare systems.

In summary, hospitals that treat more than 40 patients with rectal carcinoma per year appear to offer an advantage regarding the rate of APR. Hospitals with more than 20 patients a year had a lower intraoperative complication rate and fewer specific postoperative complications than hospitals treating fewer than 20 patients per year. This also applied to overall postoperative morbidity and hospital stay. No significant differences were found in postoperative mortality rate, resection rates, general postoperative complications and in surgery-related specific postoperative complications. The annual number of cases of rectal carcinoma needed to achieve better results with rectal surgery remains uncertain. On the basis of the present results, hospitals with a small annual caseload can achieve excellent results, and calls for a centralization of rectal surgery clearly need more critical appraisal.

Acknowledgements

Centres participating in this prospective multicentre study (listed with departmental chairman and surgeon responsible for providing the study data): G. Maskow, H.-P. Buthut (Anklam), D. Rose, H. Kranhold (Arnstadt), R. Albrecht, D. Stengl (Aue), L.-D. Schreiber, V. Weiße (Bad Langensalza), K. Bauer, D. Schmidt (Bad Liebenstein), S. Kühn, P. Kemmesies (Bad Saarow), M. Rintisch, K. Gottschall (Beeskow), J. Straßburg, M. Al-Khattab (Berlin-Friedrichshain), K. Gellert, S. Köther (Berlin-Lichtenberg), B. Günther, E. Wirth (Bischofswerda), W. Seifart, Z. Nassiri (Brandenburg), J. Reisig, U. Stradmann (Burg), I. Gastinger, M. Bereuter (Cottbus), K. Ludwig, A. Fraulhaber (Dresden), H. Diettrich, R. Kutschka (Dresden), H. D. Saeger, J. Gastmeier (Dresden), B. Goetzke, A. Wierth (Eberswalde), R. Arnrich (Erfurt), P. Schuback (Finsterwalde), St. Schwanitz (Forst), T. Manger (Frankfurt/Oder), M. Knoop, C. Elsner (Genthin), H. Schramm, T. Melchert (Gera), H. Thomas (Görlitz), K. Bickel, G. Jabour (Gotha), D. Lorenz, H. Paul (Greifswald), J. Müller, D. Briesemann (Guben), H. Dralle, G. Tonndorf (Halle/Saale), W. Asperger, B. Menschikowski (Halle/Saale), U. Rose, M. Domke (Halle/Saale), C. Richter, A. Kienast (Halle/Saale), D. Weilandt, M. Kulle (Heiligenstadt), E. Wolf, S. Frenkel (Herzberg), G. Eigendorf, J. Pfeiffer (Hildburghausen), E. Simonis, S. Kleiner (Hoyerswerda),

J. Scheele, A. Altendorf-Hofmann (Jena), W. Kärgel, B. Müller (Lauchhammer), M. Schonfelder, A. Petzold (Leipzig), A. Weimann, R. Plato (Leipzig), J. Steuber, C.-L. Weiss (Leipzig), C. Wiesner, H. Grumbt (Lübben), J. Göhler, W. Pluntke (Luckau), U. Fleck (Luckenwalde), H. Zuhlke, A. Gabler (Lutherstadt Wittenberg), W. Mokros, M. Lehmann (Magdeburg), H. Lippert, B. Falkenberg (Magdeburg), H.-J. Düwel, F. Schilling (Meiningen), F. Kühn, A. Schilling (Meißen), M. Ernst, K.-F. Ernst (Neubrandenburg), U. Kleine, C. Lange (Neuruppin), W. Georgi (Niesky), J. Rupprecht, M. Schönfelder (Nordhausen), G.-M. Fleischer, M. Ruhmer (Plauen), W. Hothorn, I. Fiedler (Pößneck), J. Marsch, H. G. Liesaus (Potsdam), H. J. C. Wenisch, A. Strauß (Potsdam), J. Bohl, B. Winter (Pritzwalk), H.-G. Ehlert, F. Schubert (Reichenbach), B. Hohaus (Riesa), H.-D. Czarnetzki, U. Helmke (Rostock), H. Rupprecht (Saalfeld/Saale), V. Bock, G. Oechel (Schmalkalden), C. Gatzweiler, J. Brecht (Senftenberg), P. Surup (Sondershausen), H. Weber, H. Frey (Sonneberg), G. Auerbeck, G. Füssel (Spremberg), M. Knoop, T. Vorwerk (Stendal), W. Hubel, G. Brettschneider (Stollberg), D. Kupczyk-Joeris, T. Kätscher (Suhl), W. Dudda, O. Breitbarth (Torgau), G. Siggelkow, R. Retzlaff (Waren/Muritz), J. Brettschneider, G. Baschleben (Weißenfels), M. Zerna (Weißwasser), T. Bolle, D. Hecht (Zeitz), M. Mory, U. Töpfer (Zschopau).

This work was supported by a grant from Pfizer Karlsruhe.

References

1 Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery *JAMA* 1998; **280**: 1747–51.

2 Gordon TA, Bowmann H, Bass EB, Lillemoe KD, Yeo CJ, Heitmiller RF *et al.* Complex gastrointestinal surgery: impact of provider experience on clinical and economic outcomes *J Am Coll Surg* 1999; **189**: 46–56.

3 Hannan EL, O'Donnell JF, Kilburn H Jr, Bernard HR, Yazici A. Investigation of the relationship between volume and mortality for surgical procedures performed in New York State hospitals. *JAMA* 1989; **262**: 503–10.

4 Hughes RG, Hunt SS, Luft HS. Effects of surgeon volume and hospital volume on quality of care in hospitals. *Med Care* 1987; **25**: 489–503.

5 Birkmeyer JD, Warshaw AL, Finlayson SR, Grove MR, Tosteson AN. Relationship between hospital volume and late survival after pancreaticoduodenectomy. *Surgery* 1999; **126**: 178–83.

6 Glasgow RE, Mulvihill SJ. Hospital volume influences outcome in patients undergoing pancreatic resection for cancer. *West J Med* 1996; **165**: 294–300.

7 Kingsnorth AN. Major HPB procedures must be undertaken in high volume quaternary centres? *HPB Surg* 2000; **11**: 359–61.

8 Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 1995, **222**: 638–45.

9 Simunovic M, To T, Theriault M, Langer B. Relation between hospital surgical volume and outcome for pancreatic resection for neoplasm in a publicly funded health care system. *Can Med Assoc J* 1999; **160**: 643–8.

10 Sosa JA, Bowmann HM, Gordon TA, Bass EB, Yeo CJ, Lillemoe KD *et al.* Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg* 1998; **228**: 429–38.

11 Pasieka JL. The surgeon as a prognostic factor in endocrine surgical diseases. *Surg Oncol Clin N Am* 2000, **9**: 13–20.

12 Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of the surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg* 1998; **228**: 320–30.

13 Choti MA, Bowman HM, Pitt HA, Sosa JA, Sitzmann JV, Cameron JL *et al* Should hepatic resections be performed at high-volume referral centers? *J Gastrointest Surg* 1998; **2**: 11–20.

14 Glasgow RE, Showstack JA, Katz PP, Corvera CU, Warren RS, Mulvihill SJ. The relationship between hospital volume and outcomes of hepatic resection for hepatocellular carcinoma. *Arch Surg* 1999, **134**: 30–5.

15 Roohan PJ, Bickell NA, Baptiste MS, Therriault GD, Ferrara EP, Siu AL. Hospital volume differences and five-year survival from breast cancer. *Am J Public Health* 1998; **88**: 454–7.

16 Ellison LM, Heaney JA, Birkmeyer JD. The effect of hospital volume on mortality and resource use after radical prostatectomy. *J Urol* 2000; **163**: 867–9.

17 Yao SL, Lu-Yao G. Population-based study of relationship between hospital volume of prostatectomies, patient outcomes, and length of hospital stay *J Natl Cancer Inst* 1999; **91**: 1950–6.

18 Porter GA, Soskolne CL, Yakimets WW, Newman SC. Surgeon-related factors and outcome in rectal cancer. *Ann Surg* 1998; **227**: 157–67.

19 Hermanek P, Wiebelt H, Staimmer D, Riedl S. Prognostic factors of rectum carcinoma – experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma. *Tumori* 1995; **81**(Suppl 3): 60–4.

20 Holm T, Johansson H, Cedermark B, Ekelund G, Rutqvist LE. Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy. *Br J Surg* 1997; **84**: 657–63.

21 McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 1991; **302**: 1501–5.

22 Meagher AP. Colorectal cancer: is the surgeon a prognostic factor? A systematic review. *Med J Aust* 1999; **171**: 308–10.

23 Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: 1. The overall picture. *Br J Surg* 1984; **71**: 12–16.

24 Simons AJ, Ker R, Groshen S, Gee C, Anthone GJ, Ortega AE

et al. Variations in treatment of rectal cancer: the influence of hospital type and caseload. *Dis Colon Rectum* 1997; **40:** 641–6.

25 The consultant surgeons and pathologists of the Lothian and Borders Health Boards. Lothian and Borders large bowel cancer project: immediate outcome after surgery. *Br J Surg* 1995; **82:** 888–90.

26 Flood AB, Scott WR, Ewy W. Does practice make perfect? Part I: The relation between hospital volume and outcomes for selected diagnostic categories. *Med Care* 1984; **22:** 98–114.

27 Flood AB, Scott WR, Ewy W. Does practice make perfect? Part II. The relation between volume and outcomes and other hospital characteristics. *Med Care* 1984; **22:** 115–25.

28 Hermanek P. Impact of surgeon's technique on outcome after treatment of rectal carcinoma. *Dis Colon Rectum* 1999; **42:** 559–62.

29 Hermanek P, Hohenberger W. The importance of volume in colorectal cancer surgery. *Eur J Surg Oncol* 1996; **22:** 213–15.

30 Hermanek P, Mansmann U, Staimmer DS, Riedl S, Hermanek P. The German experience: the surgeon as a prognostic factor in colon and rectal surgery. *Surg Oncol Clin N Am* 2000; **9:** 33–49.

31 Hermanek P, Wiebelt H, Riedl S, Staimmer D, Hermanrk P. Long-term results of surgical therapy of colon cancer. Results of the Colorectal Cancer Study Group. *Chirurg* 1994; **65:** 287–97.

32 Mörschel M, Heintz A, Junginger T. Prognostic factors in local recurrence rate after surgical therapy of rectal carcinomas. *Zentralbl Chir* 1996; **121:** 177–83.

33 Harmon JW, Tang DG, Gordon TA, Bowmann HM, Choti MA, Kaufman HS *et al.* Hospital volume can serve as a surrogate for surgeon volume for achieving excellent outcomes in colorectal resection. *Ann Surg* 1999; **230:** 404–11.

34 Blomqvist P, Ekbom A, Nyren O, Krusemo UB, Bergstrom R, Adami HO. Survival after rectal cancer: differences between hospital catchment areas. A nationwide study in Sweden. *Gut* 1999; **45:** 39–44.

35 Parry JM, Collins S, Mathers J, Scott NA, Woodman CB. Influence of volume of work on the outcome of treatment for patients with colorectal cancer. *Br J Surg* 1999; **86:** 475–81.

36 Simunovic M, To T, Baxter N, Balshem A, Ross E, Cohen Z *et al.* Hospital procedure volume and teaching status do not influence treatment and outcome measures of rectal cancer surgery in a large general population. *J Gastrointest Surg* 2000; **4:** 324–30.

37 MacRae HM, McLeod RS. Handsewn *vs.* stapled anastomoses in colon and rectal surgery: a meta-analysis. *Dis Colon Rectum* 1998; **41:** 180–9.

38 Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. *Br J Surg* 1994; **81:** 1224–6.

39 Hallbook O, Sjodahl R. Anastomotic leakage and functional outcome after anterior resection of the rectum. *Br J Surg* 1996; **83:** 60–2.

40 Carlsen E, Schlichting E, Guldvog I, Johnson E, Heald RJ. Effect of the introduction of total mesorectal excision for the treatment of rectal cancer. *Br J Surg* 1998; **85:** 526–9.

Original article

Prospective controlled trial of a standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1

P. Langer, A. Wild, I. Celik*, I. Kopp, A. Bergenfelz† and D. K. Bartsch

Department of General Surgery and *Institute of Theoretical Surgery, Philipps-University, Marburg, Germany and †Department of Surgery, University Hospital, Lund, Sweden

Correspondence to: Dr D. K. Bartsch, Department of General Surgery, Philipps-University Marburg, Baldingerstrasse, D-35043 Marburg, Germany (e-mail: bartsch@mailer.uni-marburg.de)

Background: Use of a standardized meal stimulation test has been recommended for the early diagnosis of pancreaticoduodenal endocrine tumours (PETs) in patients with multiple endocrine neoplasia type 1 (MEN 1). The diagnostic value of this test was re-evaluated.

Methods: In a prospective, controlled trial 58 standardized meal stimulation tests (563 kcal) were performed in 12 patients with MEN 1 and histologically, biochemically and/or radiologically confirmed PETs (group 1), 11 carriers of an MEN 1 mutation with no evidence of PETs (group 2) and in 27 healthy controls (group 3). Serum pancreatic polypeptide (PP) and gastrin concentrations were measured before and during the test meal.

Results: Patients in group 1 had significantly higher mean basal serum PP and gastrin concentrations than patients in group 2 and controls ($P < 0.05$). In all three groups an increase in serum PP was observed after meal stimulation, but there was no significant difference between the groups. No increase in gastrin level was found in any of the groups after meal stimulation.

Conclusion: The standardized meal stimulation test does not reliably indicate the presence of PETs in patients with MEN 1, whereas raised basal serum PP and gastrin levels do. The expensive and time-consuming meal test can be excluded from MEN 1 screening programmes.

Presented to the Millenium Meeting of the American and British Association of Endocrine Surgeons, London, UK, and Lille, France, May 2000

Paper accepted 22 May 2001

British Journal of Surgery 2001, **88**, 1403–1407

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant inherited syndrome characterized by the presence of neoplastic lesions in the parathyroid glands, the anterior pituitary gland, and in the endocrine pancreas and duodenum[1]. Endocrine tumours of the adrenals, stomach, thymus and lung can also occur but are less common. The causative *MEN 1* gene has recently been identified[2]. The *MEN 1* gene is located on chromosome 11q13 and contains ten exons that encode a 2·8-kilobase protein of 610 amino acids named menin. The *MEN 1* gene now provides the basis for predictive genetic screening of patients with MEN 1 and family members.

Screening and autopsy studies have shown that up to 80 per cent of patients with MEN 1 develop pancreaticoduodenal endocrine tumours (PETs), about half of which are malignant[3,4]. These tumours can consist of single or multiple benign or malignant neoplasms, some of which are functional and cause specific hormonal syndromes. The most common MEN 1-associated PETs are gastrinoma, insulinoma and non-functioning tumours (NFTs). PETs in MEN 1 are usually very small and multicentric. Imaging procedures often fail to visualize these tumours. Several groups have reported that serum pancreatic polypeptide (PP) and gastrin measurements are useful for screening for involvement of the endocrine pancreas. In addition, a specific meal stimulation test for PP and gastrin secretion has been developed for the early detection of PETs[5]. This 563-kcal meal stimulation test has been postulated to be most sensitive for the early detection of PETs, allowing diagnosis at least 5 years before visualization by imaging[6–8]. However, these data are not based on genetically defined groups. The aim of this study was to re-evaluate the

Table 1 Characteristics of patients with multiple endocrine neoplasia type 1 with pancreaticoduodenal endocrine tumours (group 1)

Patient	Mutation	Type of mutation	Associated PETs
1	c.1639–1640delCA/P529X	Frameshift	NFT
2	c.1770C>T/Q554X	Nonsense	Gastrinoma, insulinoma
3	c.613T>C/L168P	Missense	VIPoma
4	c.613T>C/L168P	Missense	NFT
5	c.613T>C/L168P	Missense	NFT, gastrinoma
6	c.186G>A/E26K	Missense	NFT
7	c.186G>A/E26K	Missense	NFT
8	c.1419delG/F448X	Frameshift	Gastrinoma
9	c.1390delGTCCCA/S427T	In-frame deletion	Gastrinoma
10	c.379–380InsA/Y90X	Frameshift	Gastrinoma
11	c.468A>T/K120X	Nonsense	Insulinoma, NFT
12	c.1509–1510insG, E530X	Frameshift	Insulinoma

PET, pancreaticoduodenal endocrine tumour; NFT, non-functioning tumour; VIPoma, tumour with secretion of vasoactive polypeptide

diagnostic value of the test in a prospective, controlled trial in patients with genetically confirmed MEN 1, mutation carriers and controls.

Patients and methods

Group 1 consisted of 12 patients with MEN 1 with biochemically, radiologically and/or histologically evident PETs (eight women and four men; mean age 41·2 (range 23–70) years). There were four patients with NFTs, three patients with Zollinger–Ellison syndrome (ZES), one patient with an insulinoma and one patient with a tumour secreting vasoactive intestinal polypeptide (VIPoma). One patient had both ZES and a NFT, one patient had ZES and an insulinoma, and another patient had an insulinoma and a NFT (*Table 1*). PETs in two patients were confirmed only biochemically, while PETs of six patients were visualized by various imaging procedures, including computed tomography, somatostatin receptor scintigraphy and endoscopic ultrasonography. PETs of three operated patients were confirmed by histological examination. Group 2 consisted of 11 *MEN 1* gene mutation carriers without clinical, biochemical or radiological evidence of PETs. There were four women and seven men with a mean age of 47·0 (range 31–68) years. The meal test was also performed in 27 healthy controls who comprised group 3 (13 women and 14 men; mean age 31·7 (range 21–64) years).

The meal test was performed after an overnight fast. Patients and controls received a 563-kcal meal composed of 66 g carbohydrate, 18 g protein and 22 g fat. The duration of the meal was 20 min. Blood samples were drawn at 5 min before, and 0, 10, 20 and 60 min after the start of the meal. Serum PP and gastrin were measured by competitive radioimmunoassay (Eurodiagnostica, Malmö, Sweden). Normal basal levels of PP were below 200 pg/ml and of gastrin less than 125 pg/ml. Over 28 months, 58 tests were performed in 50 individuals. Eight patients underwent two meal tests as part of an annual screening programme.

Genetic analysis

Mutation analysis of the *MEN 1* gene in 23 mutation carriers was performed as described previously[9]. In brief, constitutional DNA was used for analysis of the nine coding exons of the *MEN 1* gene by single-strand conformational variant analysis and direct sequencing. Sequencing was performed either with the Sequi-Therm™ kit (Biozym, Hessisch Oldendorf, Germany) or by Taq cycle sequencing using an automated sequencer (ABI 310 Genetic Analyser, ABI-PRISM®; Perkin Elmer, Foster City, California, USA).

Statistical analysis

Results are expressed as mean(s.d.) unless otherwise stated. PP and gastrin serum concentrations were compared by analysis of variance (Kruskal–Wallis test, 2 d.f.) and Mann–Whitney *U* test. $P < 0.05$ was considered to indicate statistical significance.

Results

Genetic analysis

Twelve different *MEN 1* gene mutations could be identified in 23 patients with MEN 1. The mutations were distributed throughout the gene and comprised six frameshift mutations (E116X, P529X, F448X, Y90X, K119X, E530X), two missense mutations (L168P, E26K), two nonsense mutations (K120X, Q554X), one splice-donor site mutation (c.894–1G>A) and one in-frame deletion (S427T).

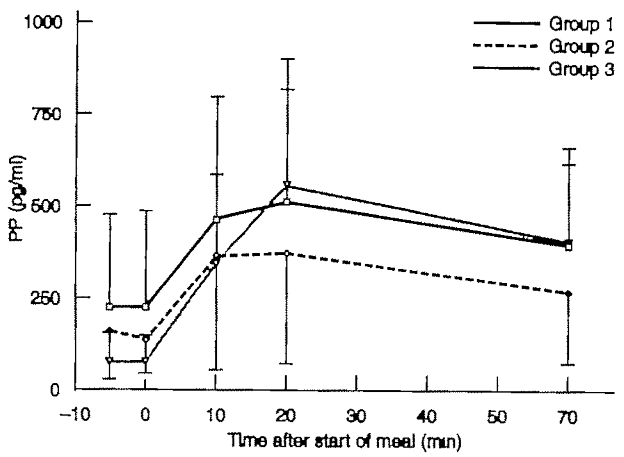


Fig. 1 Mean(s.d.) serum pancreatic polypeptide (PP) levels after meal test stimulation

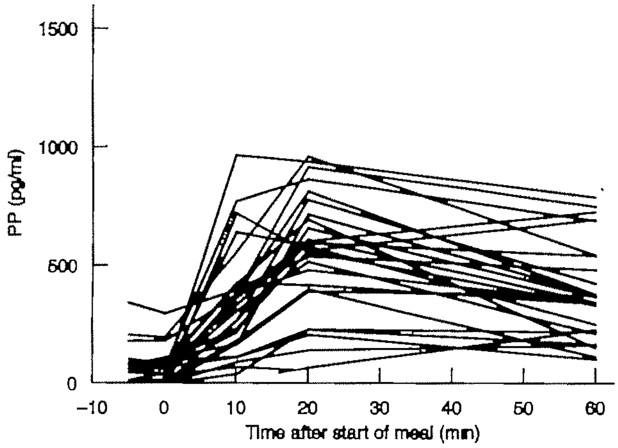


Fig. 2 Serum pancreatic polypeptide (PP) response in healthy controls (group 3) to meal test stimulation

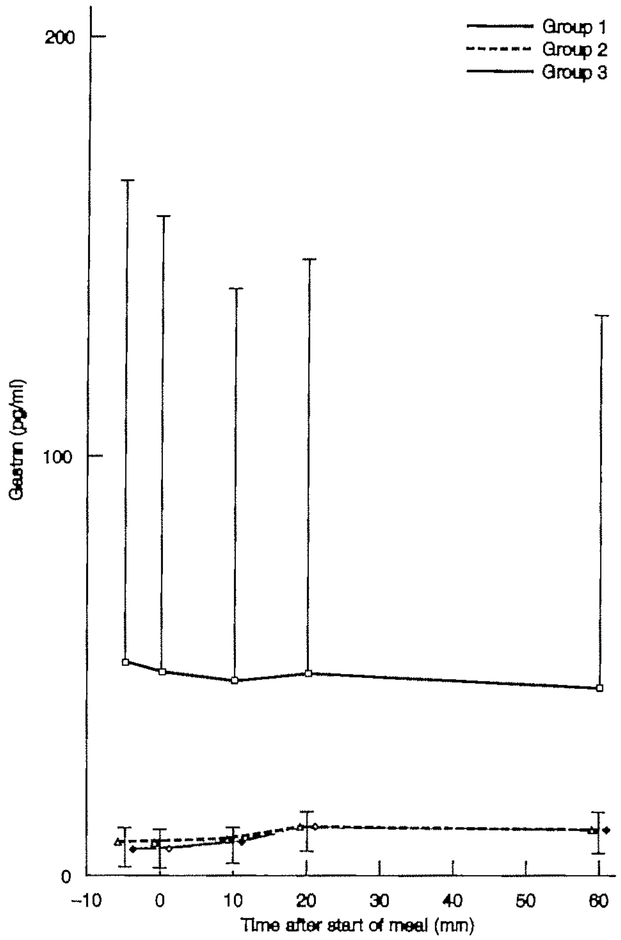


Fig. 3 Mean(s.d.) serum gastrin levels after meal test stimulation

Serum concentrations of pancreatic polypeptide

Fasting PP levels up to 200 pg/ml are considered to be within normal limits. The mean fasting PP levels in group 1 were slightly raised while those in groups 2 and 3 were normal. Four of the 12 patients in group 1 had a raised basal PP. However, in three of 11 patients in group 2 and in two of 27 healthy controls slightly raised basal PP levels were also noted. In all three groups an increase in PP after meal stimulation was observed. In each group the peak level was reached at 20 min, with a slight decrease towards 60 min (*Fig. 1*). Surprisingly, the highest PP levels after stimulation occurred in the control group at 20 min. Six of 27 healthy controls had a PP level higher than 700 pg/ml at 20 min. There were no statistically significant differences overall between the groups after meal stimulation (*Fig. 1*). It is also of note that in each group a few individuals did not respond to the meal. This caused wide variance in PP concentration within each group (*Figs 1* and *2*).

Serum concentrations of gastrin

Basal gastrin levels were raised exclusively in patients with MEN1 and ZES, and a large standard deviation was noticed owing to a patient with ZES who had a very high fasting gastrin level (4080 pg/ml). Statistically significant differences were noted between groups 1 and 3 ($P < 0{\cdot}05$). An increase in mean gastrin level during meal stimulation was not observed in any of the groups (*Fig. 3*). Mean(s.d.) peak gastrin concentration at 20 min was 483·5(987·8) pg/ml for group 1 compared with 119·4(32·3) pg/ml for group 2 and 117·3(56·3) pg/ml for group 3.

Discussion

PETs occur in about 70 per cent of MEN 1 mutation carriers[4,10–12]. In contrast to sporadic endocrine pancreatic tumours MEN 1-associated PETs are characterized by multicentricity, histological heterogeneity and higher rates of recurrence[12,13]. About two-thirds of middle-aged patients with MEN 1 have ZES, about one-quarter have hyperinsulinism and the rest have non-functioning tumours, the glucagonoma syndrome, or the syndrome of watery diarrhoea, hypokalaemia and achlorhydria. Among younger patients NFTs are the most common. Approximately half of patients with MEN 1 develop malignant PETs that represent the most important cause of death[14]. For these reasons the authors and others favour an aggressive operative approach for PETs to eliminate symptoms and to prevent the development of metastases[13,15–17]. Early detection of PETs in *MEN 1* gene mutation carriers is of outmost importance if this strategy is followed. Identification of the *MEN 1* gene now enables all resources to be focused on the *MEN 1* gene mutation carriers, possibly resulting in more efficient detection of pancreaticoduodenal involvement. However, available imaging methods often fail to visualize small PETs[17]. Skogseid *et al.*[6,7] found that a standardized 563-kcal meal stimulation test with measurement of serum PP and gastrin responses is the most sensitive test for the early detection of MEN 1 PETs. They also stated that a pathological meal test precedes radiological detection of PETs by at least 5 years[7,8]. This test has since been widely used in MEN 1 screening programmes. However, at the time of these studies neither the *MEN 1* gene nor the chromosomal region was known, so that no clear-cut distinction could be made between affected and non-affected family members. This became even more evident when the Swedish group reported, based on mutation analysis data, false-positive stimulation by the meal test in about 10 per cent of previously investigated individuals[17]. These facts prompted the current re-evaluation of the meal test in patients with genetically confirmed MEN 1 and healthy controls.

Several groups have reported that patients with MEN 1 and known PETs frequently have raised basal serum PP levels compared with patients who have MEN 1 without pancreatic involvement and normal controls[4,12,13]. The present study confirms these results. Skogseid *et al.*[6] found only a weak response to meal stimulation in the control group, whereas all of their patients with MEN 1 and PETs had PP levels higher than the mean values plus twice the standard deviation of the normal subjects. The present study, however, observed a wide variance in the PP response to the meal stimulation in all groups investigated. One-quarter of the healthy controls in the study had a strong response to the stimulation, with highly raised PP levels. Although PP and gastrin levels were not measured at 30 min in the present study, as in Skogseid's study, it is highly unlikely that significant differences were missed at this time point because of the steep increase in the PP levels in the control group between 0 and 20 min. It remains unclear why the present study obtained different results from those of Skogseid *et al.* One might argue that among the healthy controls there may have been individuals with either MEN 1-associated pancreatic endocrine disease or sporadic pancreatic endocrine tumours that were responsible for the exaggerated PP levels after meal stimulation. The likelihood of this, however, appears negligible owing to the very low incidence of both the MEN 1 syndrome (1 : 100 000) and sporadic pancreatic endocrine tumours (0·4 : 100 000)[18].

With regard to serum gastrin levels, Skogseid *et al.*[6] reported increased basal levels in patients with MEN 1 with or without PETs. They also described significant differences between patients with MEN 1 without PETs and normal subjects, as well as between patients with MEN 1 with PETs and normal subjects after stimulation at 20 and 45min. The present data did not confirm these results. Significantly increased mean basal gastrin levels were found only in patients with MEN 1 and PETs (group 1) compared with healthy controls (group 3). In terms of mean serum gastrin level, there was almost no response to the meal test stimulation in any of the groups. Only patients with MEN 1 and ZES had raised fasting gastrin levels, which slightly increased after stimulation in one patient.

The present data confirm that basal PP and gastrin concentrations are often significantly higher in patients with MEN 1 with confirmed PETs than in normal controls. It is well known that in patients with MEN 1 increases in the level of biochemical markers, such as basal PP, can precede an imageable pancreatic tumour by up to 5 years[19]; this may account for the raised basal PP level observed in three patients in group 2. Measurement of basal serum PP and gastrin is therefore a useful tool in MEN 1 screening, even though false-positive results may occur in up to 10 per cent[19].

In summary, the standardized meal test stimulation does not reliably indicate the presence of PETs. Even in the absence of questionable accuracy of the meal test, its clinical value has been superseded by improved methods for genetic diagnosis, serum chromogranin measurements, and enhanced sensitivity of imaging methods such as endoscopic ultrasonography. Therefore, the expensive and time-consuming meal test can be omitted from MEN 1 screening programmes.

Acknowledgements

Supported by a grant from the Else-Kröner-Fresenius-Stiftung to D.K.B.

References

1. Wermer P. Genetic aspects of adenomatosis of endocrine glands. *Am J Med* 1954, **16:** 363–71.
2. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR *et al.* Positional cloning of the gene for multiple endocrine neoplasia – type 1. *Science* 1997; **276:** 404–7.
3. Shepherd JJ, Challis DR, Davies PF, McArdle JP, Teh BT, Wilkinson S. Multiple endocrine neoplasia, type 1. Gastrinomas, pancreatic neoplasms, microcarcinoids, the Zollinger–Ellison-Syndrome, lymph nodes, and hepatic metastases. *Arch Surg* 1993; **128:** 1133–42.
4. Skogseid B, Oberg K, Eriksson B, Juhlin C, Granberg D, Akerstrom G *et al.* Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type I. *World J Surg* 1996; **20:** 872–6.
5. Oberg K, Lundquist G. Meal-stimulated and atropin-inhibited secretion of pancreatic polypeptide in healthy subjects, members of MEA I families and patients with malignant endocrine tumours of the gastrointestinal tract. *Regul Pept* 1983; **5:** 273–82.
6. Skogseid B, Oberg K, Benson L, Lindgren PG, Lörelius LE, Lundquist G *et al.* A standardized meal stimulation test of the endocrine pancreas for early detection of pancreatic endocrine tumors in multiple endocrine neoplasia type 1 syndrome: five years experience. *J Clin Endocrinol Metab* 1987, **64:** 1233–40.
7. Skogseid B, Eriksson B, Lundqvist G, Lörelius LE, Rastad J, Wide L *et al.* Multiple endocrine neoplasia type 1: a 10-year prospective screening study in four kindreds. *J Clin Endocrinol Metab* 1991; **73:** 281–7.
8. Skogseid B, Oberg K. Experience with multiple endocrine neoplasia type 1 screening. *J Intern Med* 1995; **238:** 255–61.
9. Bartsch D, Kopp I, Bergenfelz A, Rieder H, Munch K, Jager K *et al.* *MEN1* gene mutations in 12 MEN1 families and their associated tumours. *Eur J Endocrinol* 1998, **139:** 416–20.
10. Ballard HS, Frame B, Hartsock RJ. Familial multiple endocrine adenoma–peptic ulcer complex. *Medicine* 1964, **43:** 481–516.
11. Eberle F, Grun R. Multiple endocrine neoplasia type 1 (MEN 1) *Ergeb Inn Med Kinderheilkd* 1981; **46:** 76–149.
12. Mignon M, Ruszniewski P, Podevin P, Sabbagh L, Cadiot G, Rigaud D *et al.* Current approach of the management of gastrinoma and insulinoma in adults with multiple endocrine neoplasia type 1. *World J Surg* 1993, **17:** 489–97.
13. Grama D, Skogseid B, Wilander E, Eriksson B, Martensson H, Cedermark B *et al.* Pancreatic tumours in multiple endocrine neoplasia type 1. clinical presentation and surgical treatment. *World J Surg* 1992, **16:** 611–19
14. Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells JA, Norton JA. Lethality of multiple endocrine neoplasia type 1. *World J Surg* 1998; **22:** 581–7.
15. Bartsch DK, Langer P, Wild A, Schilling T, Celik I, Rothmund M *et al.* Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1· surgery or surveillance? *Surgery* 2000; **128:** 958–66
16. Thompson NW. Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger–Ellison syndrome, hypoglycaemia or both. *J Intern Med* 1998; **243:** 495–500.
17. Skogseid B, Oberg K, Akerstrom G, Eriksson B, Westlin JE, Janson ET *et al.* Limited tumor involvement found at multiple endocrine neoplasia type 1 pancreatic exploration: can it be predicted by preoperative tumor localization? *World J Surg* 1998; **22:** 673–8.
18. Buchanan KD, Johnston CF, O'Hare MM, Ardill JE, Shaw C, Collins JS *et al.* Neuroendocrine tumors. A European view *Am J Med* 1986; **81:** 14–22
19. Oberg K, Skogseid B. The ultimate biochemical diagnosis of endocrine pancreatic tumours in MEN-1. *J Intern Med* 1998, **243:** 471–6.

Original article

Influence of the number of lymph nodes examined on staging of gastric cancer

H. K. Lee, H.-K. Yang, W. H. Kim*, K. U. Lee, K. J. Choe and J.-P. Kim

Departments of Surgery and *Pathology, Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-Dong, Chongno-Gu, Seoul, 110–744, Korea
Correspondence to: Dr H.-K. Yang (e-mail: hkyang@plaza.snu.ac.kr)

Background: Nodal staging for gastric cancer according to the 1997 Union Internacional Contra la Cancrum tumour node metastasis classification is based on the number of metastatic lymph nodes. The aim of this study was to evaluate whether the number of lymph nodes examined affected staging of gastric cancer.

Methods: A retrospective study was performed in 4789 consecutive patients with gastric cancer, who had undergone curative resection (R_0) from 1986 to 1995. Patients were classified according to the number of nodes examined. The number of metastatic lymph nodes and stage-stratified survival were compared.

Results: There were significant differences in the number of metastatic lymph nodes and survival in stage IIIA between patients with 15 or more lymph nodes and those with fewer than 15 nodes. In analysis restricted to patients with 15 or more nodes, stage-stratified survival did not vary significantly with lymph node yields for any stage except IIIB, in which there was a significant difference between the subgroup with fewer than 20 examined lymph nodes and patients with 35 or more nodes.

Conclusion: The number of lymph nodes examined did not significantly affect node staging of gastric cancer as long as at least 15 nodes were examined. For stage IIIB, more than 15 lymph nodes may be required for optimal staging.

Paper accepted 27 May 2001

British Journal of Surgery 2001, **88**, 1408–1412

Introduction

Although the incidence of gastric cancer is decreasing in western countries, it is still one of major cancers in the world[1]. In 1997, the revised Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) classification was adopted for gastric cancer staging. The most significant change in this revision was that N stage is based on the number of metastatic lymph nodes[2].

Lymph node status and the depth of invasion are known to be significant prognostic factors for gastric cancer[3], and lymph node status is an essential component of stage classification. Lymph node status according to the Japanese Research Society for Gastric Cancer[4] and the fourth edition (1987) of the UICC TNM classification[5] is based on the anatomical site of metastatic regional lymph nodes, as determined by their distance from the primary tumour. The assessment of the distance to the edge of the primary tumour may be complex and variable, so discrepancies in the classification have existed. In the 1997 UICC TNM classification, the node stage was based on the number of metastatic lymph nodes: carcinomas without lymph node metastases were defined as N_0, those with 1–6 metastatic regional lymph nodes as N_1, 7–15 nodes as N_2, and more than 15 nodes as N_3[2]. This number-based classification has the advantage of improved reproducibility, and provides a more accurate estimation of prognosis than the former UICC N classification[6–10]. However, one major concern about the new lymph node staging system is that the number of metastatic lymph nodes is likely to be influenced by the number of lymph nodes resected and examined. The extent of lymphadenectomy and the thoroughness of lymph node retrieval determine the number of resected lymph nodes for each specimen[11]. This study aimed to evaluate the influence of number of lymph nodes examined on the staging of gastric cancer.

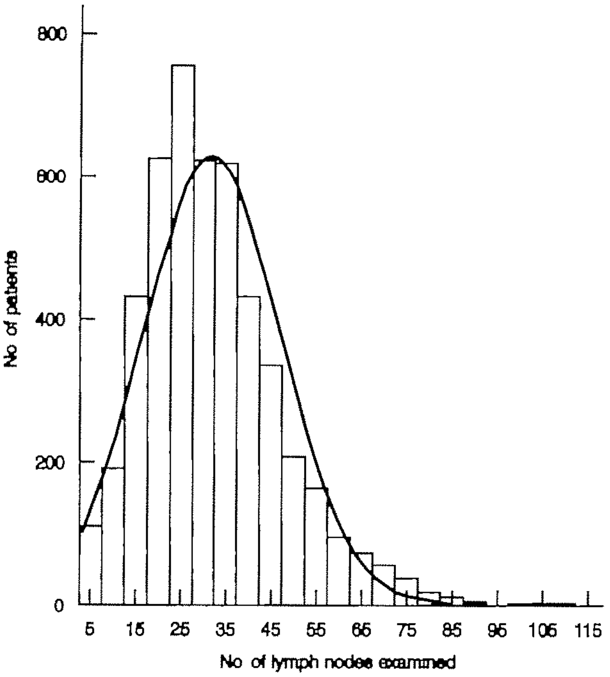
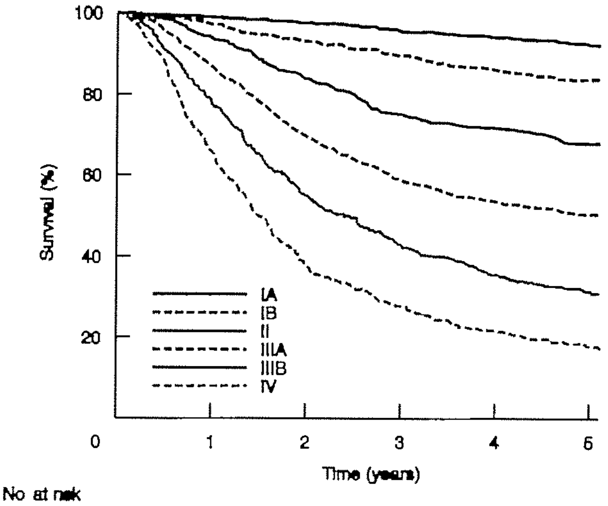


Fig. 1 Histogram showing the numerical distribution of lymph nodes examined from gastrectomy specimens. The curved line is the normal distribution curve of this histogram



No at risk						
IA	1220	1200	1100	894	729	590
IB	745	720	656	530	413	312
II	934	867	722	547	449	349
IIIA	863	743	563	421	329	273
IIIB	482	369	246	171	128	102
IV	493	316	171	102	70	45

Fig. 2 Survival curves of patients who had gastrectomy for cancer stratified by 1997 Union Internacional Contra la Cancrum stage grouping. There is a significant deterioration of survival with increased stage ($P < 0.0001$, log rank test)

Patients and methods

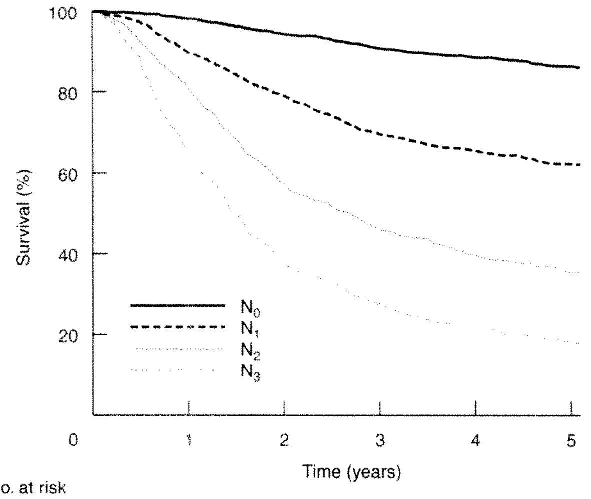
From 1986 to 1995 inclusive, 5217 consecutive patients with gastric cancer underwent surgery at the Department of Surgery, Seoul National University Hospital, Korea. Of these, 4789 patients who underwent curative resection (R_0) were included in this retrospective study. Staging was done according to the 1997 UICC TNM classification, which assumes that 15 or more lymph nodes were examined. Some 435 patients (9 per cent) with fewer than 15 lymph nodes examined were also included in the study. The aim was to determine what influence this had on assessment of nodal status. The patients were classified into subgroups according to lymph node yields. The mean number of metastatic lymph nodes for each subgroup was compared, excluding pathological stage pN_3 tumours to avoid undue influence on statistical evaluation. The stage-stratified survival, restricted by nodal yields, was analysed. Information on survival was available for 4737 (99 per cent) of the 4789 patients. The mean follow-up was 51·0 (range 1–141) months.

Survival analysis was performed using the Kaplan–Meier method and differences between groups were compared by the log rank test. Survival data are given as observed 5-year overall cumulative survival rates and include postoperative deaths. The significance of the differences in the number of metastatic lymph nodes among subgroups was determined by analysis of variance. $P < 0.05$ was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences for Windows Release 9.0 (SPSS, Chicago, Illinois, USA) statistical package.

Results

The mean age of the patients was 54·1 (range 19–88) years and the gender ratio was 2·1 : 1 in favour of men; 1415 patients (30 per cent) had T_1 tumours, 1525 (32 per cent) T_2, 1747 (36 per cent) T_3 and 102 (2 per cent) T_4 tumours. The surgical procedures performed were subtotal gastrectomy in 3637 patients (76 per cent) and total gastrectomy in 1152 (24 per cent), including combined resection.

The mean(s.d.) number of lymph nodes examined per gastrectomy specimen was 31·9(15·2) (median 30 (range 1–119)) (*Fig. 1*). Some 2646 specimens (55 per cent) demonstrated lymph node involvement and the mean(s.d.) number of metastatic lymph nodes was 8·9(9·2). A total of 435 patients had fewer than 15 lymph nodes examined; 264 (61 per cent) were node negative (N_0), of whom 164 (62 per cent) had stage IA disease. The mean(s.d.) lymph node



No. at risk						
N_0	2130	2071	1872	1530	1256	1012
N_1	1394	1244	1029	764	605	471
N_2	781	624	408	281	196	148
N_3	432	278	151	92	63	42

Fig. 3 Survival curves of patients who had gastrectomy for cancer according to the 1997 Union Internacional Contra la Cancrum lymph node stage ($P < 0.0001$, log rank test)

Table 1 Mean number of metastatic lymph nodes examined according to lymph node yields and tumour stage.

	Lymph node yield			
Depth of invasion	< 15	15–29	≥ 30	P^*
T_1	0·2(0·6) (n = 180)	0·4(1·5) (n = 649)	0·5(1·8) (n = 584)	< 0·05
T_2	1·5(2·3) (n = 122)	2·7(3·6) (n = 553)	3·4(4·1) (n = 762)	< 0·05
T_3	3·3(3·2) (n = 122)	5·0(4·4) (n = 624)	5·3(4·8) (n = 674)	< 0·05

Values are mean(s.d.). N_3 (> 15 involved nodes) specimens were excluded from the above analysis to avoid undue influence on statistical evaluation. *< 15 *versus* 15–29 and ≥30 (log rank test)

yields for each stage were as follows: IA, 28·3(13·5); IB, 31·0(14·7); II, 31·9(15·1); IIIA, 31·2(14·3); IIIB, 32·9(15·4); and IV, 42·2(16·8).

The 5-year survival rates according to stage were: stage IA, 93 per cent; stage IB, 84 per cent; stage II, 68 per cent; stage IIIA, 51 per cent; stage IIIB, 31 per cent; and stage IV, 18 per cent ($P < 0.0001$) (*Fig. 2*). The 5-year survival rates in the N_0, N_1, N_2 and N_3 groups using the 1997 lymph node staging classification were 86, 62, 36 and 19 per cent respectively. They were significantly different from each other ($P < 0.0001$) (*Fig. 3*).

There was a significant difference in the mean number of metastatic lymph nodes at each T stage between patients with 15 or more lymph nodes examined and those with fewer than 15 (*Table 1*). The number of lymph nodes examined did not influence the number of metastatic lymph nodes as long as 15 or more lymph nodes were examined. The stage-stratified survival difference between patients with 15 or more nodes examined and those with fewer with 15 was examined. Survival increased by 10 per cent for stage IB, 12 per cent for stage II and 27 per cent for stage IIIA, but this was only statistically significant for stage IIIA (*Table 2*). When the analysis was restricted to patients with 15 or more lymph nodes examined, the survival rate was not affected for any stage except IIIB, in which there was a significant difference between the subgroup with fewer than 20 examined lymph nodes and specimens with 35 or more nodes examined.

Discussion

In the 1997 UICC classification[2], recording the absolute number of metastatic lymph nodes has methodological advantages, including high reproducibility[6] and more accurate estimation of the prognosis than that based on the anatomical extent of node metastases[7–10]. In the present study, the survival curves according to N stage demon-

Table 2 Stage-stratified 5-year survival rates of patients with gastric cancer according to the number of lymph nodes examined

	5-year survival rate (%)					
No. of lymph nodes examined	IA (n = 1220)	IB (n = 745)	II (n = 934)	IIIA (n = 863)	IIIB (n = 482)	IV (n = 493)
1–14 (n = 431)	93	75	57	26*	30	–
≥ 15 (n = 4306)	93	85	69	53	31	18
15–19 (n = 527)	91	80	62	46	15	21
20–24 (n = 673)	95	79	63	51	26	13
25–29 (n = 721)	91	85	75	51	24	17
30–34 (n = 604)	92	85	63	49	32	16
35–39 (n = 563)	91	92	70	56	44†	18
≥ 40 (n = 1218)	93	87	75	58	39†	19

$^*P < 0.001$ *versus* ≥15 nodes examined; $†P < 0.05$ *versus* 15–19 nodes examined (analysis of variance) strated a significant stepwise deterioration as the number of involved lymph nodes increased. However, one major concern about the 1997 node staging system is that the number of metastatic nodes is likely to be influenced by the number of lymph nodes resected and examined. The higher probability of detecting lymph node metastases with increasing nodal yields has been confirmed by an exponential model[12]. Simply examining a small number of lymph nodes can lead to an underestimation of stage, resulting in stage migration. This is known as the Will Rogers phenomenon[13] and can cause a substantial difference in stage-specific survival rates and confound comparison of treatment results. In the 1997 UICC TNM classification it is recommended that 15 or more lymph nodes should be examined for accurate staging of gastric cancer. The present study included patients with fewer than 15 examined lymph nodes and evaluated the effect on staging. The number of metastatic lymph nodes identified and survival both increased significantly when 15 or more lymph nodes were examined. Karpeh *et al.*[14] similarly showed that survival significantly increased for stage II, IIIA and IIIB tumours when 15 or more nodes were examined. Hundahl *et al.*[15] also identified the effect of suboptimal lymph node analysis on staging: 5-year stage-stratified survival increased in patients with 15 or more lymph nodes analysed. These results are likely to be due to stage migration, and indicate that at least 15 lymph nodes are the minimum requirement for adequate lymph node staging of gastric cancer.

In survival analysis restricted to patients with at least 15 examined lymph nodes, the number did not significantly affect staging of gastric cancer. Survival did not change significantly when stratified according to five-interval nodal yields for any stage except IIIB, in which there was a significant difference. Patients with 15–19 examined nodes, who comprised about 10 per cent of all stage IIIB tumours, had a significantly lower 5-year survival rate than those with 35 or more nodes examined. This difference may reflect that an increase in the number of nodes examined increased the number of positive nodes, and therefore altered the stage. Fewer than 20 examined nodes may be inadequate for assignment to stage IIIB, which is defined as 7–15 involved lymph nodes.

The number of lymph nodes examined is affected not only by the extent of lymphadenectomy[16–20] but also by techniques and intensity for the retrieval of lymph nodes[11,21,22], and personal variation[12]. At least 15 lymph nodes is an acceptable minimum for adequate staging as long as extended lymphadenectomy is routinely performed with curative intent. In the present study, 9 per cent of patients analysed had fewer than 15 nodes examined, a much lower percentage than that in western surgical centres. Some 38 per cent of patients with fewer than 15 lymph nodes examined had node-negative early gastric cancer (stage IA). These patients had no stage-specific survival difference according to lymph node yields (including fewer than 15). Therefore, fewer than 15 nodes may be reasonable to determine N stage in node-negative early gastric cancer. Kranenbarg *et al.*[23] reported that a minimum of five consecutive negative lymph nodes is reliable in this situation. Further studies are warranted to establish the minimum requirement for N_0 staging of gastric cancer.

References

1 Muir CS, Harvey JC. Cancer of the stomach: overview. In: Sugimura, T, Sasako, M, eds. *Gastric Cancer*. Oxford: Oxford University Press, 1997: 3–21.

2 Sobin LH, Wittekind Ch, eds. *TNM Classification of Malignant Tumours. International Union Against Cancer (UICC)*. 5th ed. New York: Wiley–Liss, 1997.

3 Kim JP, Kim YW, Yang HK, Noh DY. Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. *World J Surg* 1994; **18**: 872–7.

4 Japanese Research Society for Gastric Cancer. *Japanese Classification of Gastric Carcinoma*. 1st English ed. Tokyo: Kanehara, 1995.

5 Hermanek P, Sobin LH, eds. *TNM Classification of Malignant Tumors. International Union Against Cancer (UICC)*. 4th ed. Berlin: Springer, 1987.

6 Hermanek P, Altendorf-Hofmann A, Mansmann U, Dworak O, Wittekind C, Hohenberger W. Improvements in staging of gastric carcinoma from using the new edition of TNM classification. *Eur J Surg Oncol* 1998; **24**: 536–41.

7 Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K *et al.* The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. *J Am Coll Surg* 1998; **187**: 597–603.

8 Yoo CH, Noh SH, Kim YI, Min JS. Comparison of prognostic significance of nodal staging between old (4th edition) and new (5th edition) UICC TNM classification for gastric carcinoma. International Union Against Cancer. *World J Surg* 1999; **23**: 492–8.

9 Roder JD, Bottcher K, Busch R, Wittekind C, Hermanek P, Siewert JR. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. *Cancer* 1998; **82**: 621–31.

10 Fujii K, Isozaki H, Okajima K, Nomura E, Niki M, Sako S *et al.* Clinical evaluation of lymph node metastasis in gastric cancer defined by the fifth edition of the TNM classification in comparison with the Japanese system. *Br J Surg* 1999; **86**: 685–9.

11 Bunt AMG, Hermans J, van de Velde CJH, Sasako M, Hoefsloot FAM, Fleuren G *et al.* Lymph node retrieval in a randomized trial on western-type *versus* Japanese-type surgery in gastric cancer. *J Clin Oncol* 1996; **14**: 2289–94.

12 Bunt AMG, Hogendoorn PCW, van de Velde CJH, Bruijn JA,

Hermans J. Lymph node staging standards in gastric cancer. *J Clin Oncol* 1995; **13:** 2309–16.

13 Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312:** 1604–8.

14 Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than number? An analysis of 1038 patients. *Ann Surg* 2000; **232:** 362–71.

15 Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of US gastric carcinoma patients treated with gastrectomy. Fifth Edition American Joint Committee on Cancer Staging, proximal disease, and the 'different disease' hypothesis. *Cancer* 2000; **88:** 921–32.

16 Siewert JR, Böttcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systemic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. *Br J Surg* 1993; **80:** 1015–18.

17 Soga J, Ohyama S, Miyashita K, Suzuki T, Nashimoto A, Tanaka O *et al.* A statistical evaluation of advancement in gastric cancer surgery with special reference to the significance of lymphadenectomy for cure. *World J Surg* 1988; **12:** 398–405.

18 Ichikura T, Tomimatsu S, Okusa Y, Uefuji K, Tamakuma S. Comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage based on their location in patients with gastric cancer. *J Clin Oncol* 1993; **11:** 1894–900.

19 de Manzoni G, Verlato G, Guglielmi A, Laterza E, Genna M, Cordiano C. Prognostic significance of lymph node dissection in gastric cancer. *Br J Surg* 1996; **83:** 1604–7.

20 Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT *et al.* Randomized comparison of morbidity after D_1 and D_2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; **345:** 745–8.

21 Noda N, Sasako M, Yamaguchi N, Nakanishi Y. Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. *Br J Surg* 1998; **85:** 831–4.

22 Bunt AMG, Hermans J, Smit VTHBM, van de Velde CJH, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995; **13:** 19–25.

23 Klein Kranenbarg E, Hermans J, van Krieken JHJM, van de Velde CJH. Evaluation of the 5th edition of the TNM classification for gastric cancer: improved prognostic value. *Br J Cancer* 2001; **84:** 64–71.

Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark

T. Filtenborg Tvedskov, M. S. Rasmussen and P. Wille-Jørgensen

Centre for Clinical Thrombosis Research, Department of Surgical Gastroenterology, HS Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark
Correspondence to: Dr M. S. Rasmussen, Department of Surgical Gastroenterolgy 435, HS Hvidovre Hospital, DK-2650 Hvidovre, Denmark (e-mail: msr@dadlnet.dk)

Background: The aim of this study was to determine the current use of thromboprophylaxis for laparoscopic surgery in Denmark.

Methods: Postal questionnaires were sent to all Danish surgical departments that performed laparoscopic surgery according to the National Laparoscopic Cholecystectomy Database.

Results: There was a written protocol for thromboprophylaxis in 93 per cent of the responding departments. In 37 per cent thromboprophylaxis was used for all patients undergoing laparoscopic surgery; only 7 per cent used thromboprophylaxis sporadically. All departments used low molecular weight heparin, 74 per cent in combination with graduated compression stockings. The criteria for using thromboprophylaxis varied greatly; in many departments conversion of the procedure to an open operation was not considered a criterion. Some 20 per cent of the departments reported previous thromboembolic complications following laparoscopic surgery.

Conclusion: Despite the widespread use of thromboprophylaxis, symptomatic thromboembolic complications were reported from several departments. Further studies are needed to determine whether laparoscopic surgery should be considered a high-risk procedure.

Paper accepted 6 May 2001

British Journal of Surgery 2001, **88**, 1413–1416

Introduction

The risk of thromboembolic complications in relation to general surgery is well known[1]. To reduce this risk, thromboprophylaxis is advised routinely in general surgery[2]. The risk of thromboembolic complications in relation to laparoscopic surgery is less well known[3]. Compared with open surgery, the risks of laparoscopic surgery might be expected to be lower owing to reduced surgical stress and earlier mobilization[4]. However, there are increases in intra-abdominal pressure caused by pneumoperitoneum, and the reverse Trendelenburg position impedes venous return leading to venous stasis in the legs[5]. Laparoscopic surgery has also been shown to induce significant hypercoagulability[6,7]. These facts indicate that the risk of thromboembolic complications after laparoscopic surgery might be as high as those associated with open surgery.

Few studies have described the incidence of thromboembolic complications after laparoscopic surgery. The reported incidence varies from 0 to 55 per cent, probably the result of failure of systematic screening for deep vein thrombosis (DVT) and differences in methodology[3,8–10]. Systematic screening of all patients with venous duplex imaging was performed in one small study[8]; 11 of 19 patients had a DVT. In existing studies, a variable number of the patients received thromboprophylaxis[3,9,10]. There was inconsistency in the use of thromboprophylaxis in connection with laparoscopic surgery in surgical departments in the UK, in a report from 1997[10].

The aim of the present study was to determine current use of thromboprophylaxis in relation to laparoscopic surgery in Denmark.

Methods

Postal questionnaires were sent to surgical departments in Denmark that are registered as performing laparoscopic surgery according to the National Laparoscopic Cholecystectomy Database. A reminder letter was sent to non-responders after 4 months.

For each department the following data were sought: type of laparoscopic surgery done in the department; length of admission after laparoscopic surgery; whether a written protocol for the use of thromboprophylaxis existed; indications for the use of thromboprophylaxis; type of thromboprophylaxis used in the department; start and duration of thromboprophylaxis; satisfaction with the use of thromboprophylaxis; complications of thromboprophylaxis; and previous thromboembolic complications after laparoscopic surgery in the department.

A written protocol had to be preorganized, and outline the type of thromboprophylaxis a given patient should receive, taking into consideration the various risk factors.

Results

The questionnaires were sent to 55 surgical departments. Replies were received from 46; in two departments laparoscopic surgery was not performed at all, and these were excluded. The response rate was therefore 87 per cent (46 of 53 departments). Forty-three (93 per cent) of the responding departments employed thromboprophylaxis using a written protocol. In 17 departments thromboprophylaxis was used for all patients undergoing laparoscopic surgery, in 26 it was prescribed selectively, and in only three departments was thromboprophylaxis used sporadically. Low molecular weight heparin (LMWH) was employed in all 46 departments; in 34 (74 per cent) graduated compression stockings were also used (*Table 1*).

In departments where thromboprophylaxis was applied selectively, various criteria were used (*Table 2*). When age was used as indication for prophylaxis, 40 years was most often reported as the limit. If operating time was used as a criterion, over 30 min was often reported as the limit but many departments did not give a specific time.

Table 1 Use of thromboprophylaxis in 46 surgical departments surveyed

	No. of departments
Written protocol	43 (93)
Used for all patients	17 (37)
Used selectively	26 (57)
Sporadic use of thromboprophylaxis	3 (7)
Type of prophylaxis	
LMWH	46 (100)
Graduated compression stockings	34 (74)
Duration of thromboprophylaxis	
1 day	14 (30)
2–4 days	5 (11)
5–7 days	5 (11)
Until discharge	11 (24)
Until mobilization	10 (22)
Individually	1 (2)

Values in parentheses are percentages. LMWH, low molecular weight heparin

In all departments thromboprophylaxis was started before operation. The duration varied from 1 to 7 days, or until mobilization or discharge (*Table 1*). When prophylaxis was given for 5–7 days, it was stopped if the patient was discharged earlier. When prophylaxis was given until discharge, the duration was usually 1–2 days.

All departments were satisfied with their administration of thromboprophylaxis. None experienced any serious adverse events.

Thromboembolic complications following laparoscopic surgery were described by nine departments (20 per cent). Pulmonary embolism had been experienced in five departments, DVT in two and coronary occlusion in one; one department reported that 'few clinical incidences of thromboembolic complications' were seen. In these nine departments thromboprophylaxis was currently administered according to a written protocol.

Discussion

The high response rate to this questionnaire allows conclusions to be drawn about the use of thromboprophylaxis in relation to laparoscopic surgery in Denmark. It should be kept in mind that the non-responding departments could be disregarding the importance of thromboprophylaxis.

In 1995 the majority (92 per cent) of surgical departments in Denmark used thromboprophylaxis routinely when performing open abdominal surgery[11]. The current use of thromboprophylaxis in relation to laparoscopic surgery was found to be just as common, as 93 per cent of the responding departments used thromboprophylaxis accord-

Table 2 Indications for using thromboprophylaxis during laparoscopic surgery in the 26 departments in which prophylaxis was used selectively

	No. of departments
Previous thromboembolic complications	23
Age	23
Obesity (> 20 per cent BMI)	19
Malignancy	14
Acute laparoscopic surgery (within 24 h)	9
Prolonged operating time	11
Coexisting varicose veins	11
Conversion to open operation	4

BMI, body mass index

ing to a written protocol. In a similar survey among surgeons in the UK in 1997, the overall use of thromboprophylaxis was 94 per cent; 74 per cent of the surgeons gave thromboprophylaxis to all their patients and 20 per cent to some patients[10]. The response rate in the UK survey was somewhat lower (69 per cent). In contrast to the Danish surgical departments, the majority of the UK surgeons used unfractionated heparin; only 30 per cent used LMWH. This is probably due to the higher treatment costs for LMWH in the UK in 1997, whereas there is currently no difference in the cost of these treatments in Denmark.

The optimal thromboprophylaxis for patients undergoing laparoscopic surgery might be LMWH and graduated compression stockings[1,12], the combination most commonly used in Denmark.

The criteria for using thromboprophylaxis varied greatly. Few studies describe the risk factors for developing thromboembolic complications after laparoscopic surgery[9], whereas the risk factors in general surgery are well known[13]. Risk factors were not used as the indication for applying thromboprophylaxis in most of the departments, as laparoscopic surgery was considered a minimally invasive procedure. The risk of thromboembolic complications could be as high as in open surgery, and the same criteria for the use of thromboprophylaxis could be used.

In the 26 departments where thromboprophylaxis was not used for all laparoscopic operations, only four (15 per cent) found it necessary to use thromboprophylaxis when a laparoscopic operation was converted to open surgery. In the UK study, 38 per cent used conversion to open surgery as an indication for thromboprophylaxis[10]. Conversion prolongs the operating time, which increases the risk of thrombosis[14].

In the present survey, thromboprophylaxis was started before operation in all departments, reflecting that fact that most DVTs develop soon after operation, so that prophylaxis should be given as early as possible[8]. In contrast, the duration of the prophylaxis varied considerably. The optimal duration of thromboprophylaxis after laparoscopic surgery still needs to be investigated.

Despite the use of a written protocol in the majority of the departments, 20 per cent reported thromboembolic complications. More than half of these departments had seen a pulmonary embolism. In the UK survey only 9 per cent had experienced thromboembolic complications after laparoscopic surgery[10]. The real incidence of thromboembolic complications could be higher due to asymptomatic cases, and complications appearing after discharge. In the Danish National Laparoscopic Cholecystectomy Database, 26 per cent of the departments have reported symptomatic thromboembolic complications. The number of patients reported with a complication was 19 after 19 640 laparoscopic cholecystectomies, an incidence of 0·1 per cent. This incidence is comparable to that found by Lindberg *et al.*[3].

A high number of the reported events were of pulmonary embolism, indicating that laparoscopic surgery is associated with a significant increase in thromboembolism.

The majority of patients undergoing laparoscopic surgery in Denmark receive thromboprophylaxis with LMWH and graduated compression stockings administered according to a written protocol. Despite the widespread use of thromboprophylaxis, symptomatic thromboembolic complications were reported from several departments. Further scientific studies should be done to determine the optimal use of thromboprophylaxis after laparoscopic surgery and to prove whether laparoscopic surgery should be considered a high-risk procedure.

Acknowledgements

The authors thank Dr Svend Adamsen, Bispebjerg Hospital, for the data from the Danish National Laparoscopic Cholecystectomy Database.

References

1 National Institutes of Health Consensus Development. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; **256**: 744–9.

2 Thrombotic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992, **305**: 567–74.

3 Lindberg F, Bergqvist D, Rasmussen I. Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature. *Surg Laparosc Endosc* 1997; **7**: 324–31.

4 Bailey RW, Zucker KA, Flowers JL, Scovill WA, Graham SM, Imbembo AL. Laparoscopic cholecystectomy. Experience with 375 consecutive patients. *Ann Surg* 1991; **214**: 531–40.

5 Jorgensen JO, Gillies RB, Lalak NJ, Hunt DR. Lower limb venous hemodynamics during laparoscopy. an animal study. *Surg Laparosc Endosc* 1994; **4**: 32–5.

6 Caprini JA, Arcelus JI, Laubach M, Size G, Hoffman KN, Coats RW II *et al.* Postoperative hypercoagulability and deep-vein thrombosis after laparoscopic cholecystectomy. *Surg Endosc* 1995; **9**: 304–9.

7 Dexter SPL, Griffith JP, Grant PJ, McMahon MJ. Activation of coagulation and fibrinolysis in open and laparoscopic cholecystectomy. *Surg Endosc* 1996; **10**: 1069–74.

8 Patel MI, Hardman DTA, Nicholls D, Fisher CM, Appleberg M. The incidence of deep venous thrombosis after laparoscopic cholecystectomy. *Med J Aust* 1996; **164**: 652–6.

9 Mayol J, Vincent-Hamelin E, Sarmiento JM, Oshiro EO, Diaz Gonzalez J, Tamayo FJ *et al.* Pulmonary embolism following laparoscopic cholecystectomy: report of two cases and review of the literature *Surg Endosc* 1994; **8**: 214–17.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk*

A normal appendix found during diagnostic laparoscopy should not be removed (*Br J Surg* 2001; 88: 251–4)

Sir

We read this paper with interest and agree that the diagnosis of appendicitis can be difficult in patients with atypical symptoms. However, we question the title of the paper as, in certain cases, it cannot be assumed that a grossly normal appendix is unrelated to symptoms. Evidence is growing in the area of neuroimmune appendicitis and studies have shown that, despite normal routine histology, there can be morphological and phenotypical changes within the enteric nervous system in patients with recurrent symptoms[1].

The mechanism underlying these symptoms is not fully understood but it may be that an initial episode of subacute inflammation in the appendix damages the enteric nervous system which then causes episodic pain in response to minor stimuli, such as luminal distension or food debris. This may explain why 9 per cent of patients in the paper by van den Broek *et al.* had recurrent symptoms and in this situation we should be swayed to remove a grossly normal appendix despite an otherwise normal laparoscopy.

J. Simpson
J. H. Scholefield
Faculty of Medicine and Health Sciences
University of Nottingham
Queen's Medical Centre
Nottingham NG7 2UH
UK

1 Di Sebastiano P, Fink T, Di Mola FF, Weihe E, Innocenti P, Friess H *et al.* Pathology of neuroimmune appendicitis. *Lancet* 1999; 354: 461–6.

Re-excision of soft tissue sarcoma after inadequate initial operation (*Br J Surg* 1995; 82: 278–9)

Sir

In 1995 we published our results of primary re-excision of soft tissue sarcoma after inadequate initial surgery. This regimen was introduced following a report by Hays *et al.*[1] which showed residual tumour in 49 per cent of patients after unplanned assumed total excision of soft tissue sarcoma. We reported a mean follow-up of 32 months and a 7 per cent local recurrence rate. After a further 7 years of follow-up we would like to present the long-term results of this procedure.

Initially 67 patients underwent re-excision after unplanned resection of a soft tissue sarcoma not achieving wide resection margins. The surgical area was excised *en bloc* and in 45 per cent of the specimens residual tumour was found. After a median follow-up of 15 months, 84 per cent of patients ($n = 56$) remained free of local recurrence. Eleven patients (16 per cent) developed local recurrence after a median (range) of 27 (3–66) months. Of the latter, eight of the primary operations had been classified as R_0 and three patients have had marginal resections (R_1). Four of the 11 recurrent tumours were grade 2, four were grade 3, and three recurrences were highly differentiated.

Thirteen patients developed distant metastases after a median (range) of 33 (1–112) months. Five of the 11 patients with local recurrence developed distant metastases, compared with eight of 45 patients without local recurrence ($P < 0.05$). Primary tumours in these patients had been highly differentiated in two, grade 2 in seven and grade 3 in four. At the end of follow-up, 52 patients (78 per cent) were alive with no evidence of disease. Six patients died from other causes and nine deaths were tumour related. The cumulative survival times (Kaplan–Meier method) after 5 and 10 years were 91 and 84 per cent respectively.

Even after a long-term follow-up of 10 years, 84 per cent of our patients remained free of local recurrence. Local recurrence and distant metastases developed at any grade, and distant metastases developed more often in patients with local recurrence. We surmise that re-excision in cases of inadequate primary operation of a soft tissue sarcoma is the treatment of choice.

M. Peiper
C. Zornig
S. Schröder
Department of Surgery
University Hospital Hamburg Eppendorf
Martinistrasse 52
20246 Hamburg
Germany

1 Hays DM, Lawrence W Jr, Wharam M, Newton W Jr, Ruymann FB, Beltangady M *et al.* Primary reexcision for patients with 'microscopic residual' tumor following initial excision of sarcomas of trunk and extremity sites. *J Pediatr Surg* 1989; 24: 5–10.

An unexpected liver secondary (*Br J Surg* 2001; 88: 627–8)

Sir

We would like to question the role of intraoperative biopsy of the hepatic lesion at the time of primary colorectal surgery. Although significantly under-reported, biopsy of hepatic metastases carries a definite risk of needle tract seeding and transcoelomic spread of tumour[1,2]. The combination of intraoperative inspection, palpation and intraoperative ultrasonography in experienced hands has a sensitivity of 98 per cent and a specificity of 95 per cent[3]. In combination with a raised carcinoembryonic antigen level, biopsy of the hepatic lesion is an unnecessary hazard. In the small percentage of patients where there is still diagnostic uncertainty, it is our practice to embark on a period of observation and re-imaging with computed tomographic arterial portography and magnetic resonance imaging after 3 months.

At the most recent International Hepato-Pancreatico-Biliary Association meeting in Brisbane, a symposium on the issue of concomitant rectal and liver resection came to the conclusion that a one-stage procedure was advisable only if both operations were straightforward and could be performed with minimal morbidity.

S. T. Yeung
M. Rees
Department of Hepatobiliary Surgery
The North Hampshire Hospital
Aldermaston Road
Basingstoke RG24 9NA
UK

1 John TG, Garden OJ. Needle track seeding of primary and secondary liver carcinoma after percutaneous liver biopsy. *HPB Surg* 1993; **6:** 199–203.
2 Scheele J, Altendorf-Hofmann A. Tumor implantation from needle biopsy of hepatic metastases. *Hepatogastroenterology* 1990; **37:** 335–7.
3 Schmidt J, Strotzer M, Fraunhofer S, Boedeker H, Zirngibl H. Intraoperative ultrasonography *versus* helical computed tomography and computed tomography with arterioportography in diagnosing colorectal liver metastases: lesion-by-lesion analysis. *World J Surg* 2000; **24:** 43–7.

Procalcitonin strip test in the early detection of severe acute pancreatitis (*Br J Surg* 2001; 88: 222–7)

Sir

Kylänpää-Bäck and colleagues describe good results for the procalcitonin strip test in the early prediction (not detection) of severe acute pancreatitis. I would strongly support the routine use of a single marker for the early prediction of severe acute pancreatitis. The authors claim that the procalcitonin strip test is superior to other single markers, such as serum or plasma C-reactive protein (CRP) which is routinely available in virtually all clinical chemistry laboratories, and urinary trypsinogen activation peptide (TAP) for which an automated assay is currently being developed.

The study that was conducted, however, has not provided data to support this conclusion. Although the authors undertook a head-to-head comparison with CRP, raw data on accuracy were not provided and there were no obvious statistically significant differences. If these analyses were performed it would be useful to know the results. Indeed, Müller *et al.*[1] found no statistical differences between serum procalcitonin and serum CRP levels in the early differentiation between mild and acute pancreatitis.

Direct comparison between the study of Kylänpää-Bäck *et al.* and the recent multicentre urinary TAP study[2] is not strictly possible. In the former study the median delay in hospital admission of all patients with acute pancreatitis was 24 h, compared with 13 h in the TAP study. Such a difference is extremely important because severity markers are exquisitely time-sensitive. For example, procalcitonin does not peak for at least 24 h after the onset of acute pancreatitis[3] (and 72–96 h in the case of CRP[2,3]), whereas TAP concentration rises immediately[3]. Thus, the longer the median hospital admission, the more likely that all markers would have peaked or plateaued and with few, if any, significant differences discernible. In order to overcome this confounding variable, prospective studies should standardize the results from the time of symptom onset[1–3]. Unfortunately the study by Kylänpää-Bäck *et al.* failed to do this, invalidating their comparison between procalcitonin and TAP. Indeed, it would be surprising to find that procalcitonin is a better 'early' marker for predicting severity when its concentration peaks only 24 h or so after that of TAP[2,3].

The procalcitonin strip test provides four different semi-quantitative values but which one of these was used for prognostication (*Table 2*)? The 'cut-off' values for serum CRP and the Ranson and Acute Physiology And Chronic Health Evaluation II scores were set *pre hoc* from published literature. Was the procalcitonin 'cut-off' value set *pre hoc* or *post hoc*? Clearly, if variable scores were used and/or set *post hoc*, the conclusions would be less certain.

J. P. Neoptolemos
Department of Surgery
Royal Liverpool University Hospital
Daulby Street
Liverpool L69 3GA
UK

1 Müller CA, Uhl W, Printzen G, Gloor B, Bischofberger H, Tcholakov O *et al.* Role of procalcitonin and granulocyte colony stimulating factor in the early prediction of infected necrosis in severe acute pancreatitis. *Gut* 2000; **46:** 233–8.
2 Neoptolemos JP, Kemppainen EA, Mayer JM, Fitzpatrick JM, Raraty MGT, Slavin J *et al.* Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. *Lancet* 2000; **355:** 1955–60.
3 Oezcueruemez-Porsch M, Kunz D, Hardt PD, Fadgyas T, Kress O, Schulz HU *et al.* Diagnostic relevance of interleukin pattern, acute-phase proteins, and procalcitonin in early phase of post-ERCP pancreatitis. *Dig Dis Sci* 1998; **43:** 1763–9.

Stapled haemorrhoidectomy: pain or gain (*Br J Surg* 2001; 88: 1–3)

Sir

The term 'stapled haemorrhoidectomy', used widely to describe the procedure for prolapse and haemorrhoids, as first described by Longo[1], is a misnomer. Longo did not propose 'stapled haemorrhoidectomy' as a name for this technique as it does not remove them but relies on a stapling device to 'hitch up' the haemorrhoids and associated skin tags. We described the stapled haemorrhoidectomy[2,3] and were surprised that Seow-Choen failed to mention our technique.

The method of closed haemorrhoid excision proved to be simple and effective[2] and in a randomized trial resulted in less postoperative pain, faster wound healing and higher patient satisfaction, compared with Ferguson's method[3]. We suggest that our technique satisfies the tenets of Milligan-Morgan in that it removes the haemorrhoids and associated skin tags but, unlike the last operation, an open wound is not created. As for the procedure for prolapse and haemorrhoids, our technique also involves a relatively expensive stapling device, but reduced pain and faster wound healing mean that the patient can return to employment earlier. Predictably, the reported merits of the procedure have generated much debate in that they reflect short-term results[4]. The long-term outcome might reinforce the adage that 'what goes up must come down' and, as Cheetham *et al.* suggest, it is important for those using the procedure to continue long-term follow-up. We propose that this technique should be termed Longo's operation or PPH (procedure for prolapse and haemorrhoids), and not stapled haemorrhoidectomy.

A. O'Bichere
K. Khalil
D. Sellu
Department of Surgery
Ealing Hospital
Uxbridge Road
Southall UB1 3HW
UK

1 Longo A. Treatment of haemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with a circular-suturing device: a new procedure. *Proceedings of the Sixth World Congress of Endoscopic Surgery*, Rome, Italy, 3–6 June 1998: 777–84.
2 O'Bichere A, Laniado M, Sellu D. Stapled haemorrhoidectomy: a feasible day-case procedure. *Br J Surg* 1998; **85**: 377–8.
3 Khalil KH, O'Bichere A, Sellu D. Randomized clinical trial of sutured *versus* stapled closed haemorrhoidectomy. *Br J Surg* 2000; **87**: 1352–5.
4 Cheetham MJ, Mortensen NJ, Nystrom PO, Kamm MA, Phillips RK. Persistent pain and faecal urgency after stapled haemorrhoidectomy. *Lancet* 2000; **356**: 730–3.

Role of resection and primary anastomosis of the left colon in the presence of peritonitis (*Br J Surg* 2000; 87: 1580–4)

Sir

Thank you for the opportunity to reply to Dr Menon[1]. We initially performed left colonic resection and primary anastomosis (RPA) in patients with only colonic obstruction and localized peritonitis[2]. From the start of the study in 1994, RPA was offered to selected patients with diffuse peritonitis in an entirely prospective manner. This study was not a randomized trial and the only difference between the groups was the stage of peritonitis. We believe there was no bias or any invalid comparison between patients with localized and diffuse peritonitis. We recently observed in a multivariate analysis of prognostic factors in patients with left colonic peritonitis that grade did not influence postoperative mortality[3]. Of the two immunocompromised patients included in the RPA group, one had Horton's disease and the other chronic obstructive pulmonary disease; both were taking low-dose glucocorticoid therapy.

Left colonic perforation is an uncommon complication in patients with Crohn's disease and ulcerative colitis, and is usually observed after intensive immunosuppressive treatment. These patients should never be considered for a one-stage procedure.

Those with perforated tumours had lesions in the sigmoid and rectosigmoid regions. In emergency operations when a one-stage procedure is possible, a stoma would be fashioned following the same criteria as in elective surgery. All anastomoses were stapled.

S. Biondo
Department of Surgery
Colorectal Unit
Hospital de Bellvitge
08907 Barcelona
Spain

1 Menon VS. Role of resection and primary anastomosis of the left colon in the presence of peritonitis. *Br J Surg* 2001; **88**: 889.
2 Biondo S, Jaurrieta E, Jorba R, Moreno P, Farran L, Borobia F *et al.* Intraoperative colonic lavage and primary anastomosis in peritonitis and obstruction. *Br J Surg* 1997; **84**: 222–5.
3 Biondo S, Ramos E, Deiros M, Martı Ragué J, De Oca J, Moreno P *et al.* Prognostic factors for mortality in left colonic peritonitis: a new scoring system. *J Am Coll Surg* 2000; **191**: 635–42.

Book reviews

Endocavity MRI of the pelvis

N. M. deSouza (ed.)

285 × 220 mm. Pp. 114. Illustrated. 2001. Amsterdam: Harwood Academic. £38·00.

This is a detailed evaluation of endocoil use in magnetic resonography of the pelvis. Why endocoils might be valuable is described in the first chapter on basic physics, always the least read. To put this into perspective, all magnets have coils. There is one built into the main housing – the body coil. Phased-array coils are now routinely used for pelvic imaging, and these are wrapped around the patient like a corset. These coils provide the radiofrequency pulses that are manipulated to give the different sequences (i.e. T1 or T2) for varying the tissue contrast. Spatial resolution depends on the ratio of signal from a defined volume of tissue compared to background noise. Endocoils provide an opportunity to increase the signal : noise ratio close to the coil, allowing thinner sections and smaller voxel size so that definition is improved. The trade-off is reduced depth of penetration. Endocoils, therefore, give increased resolution within a limited field, and may be used to advantage within the anorectum or vagina to yield exquisite anatomical detail of these and intimately related structures.

There are chapters on the uterine cervix, prostate, bladder neck, urethra and seminal vesicles, rectum and anal sphincter. The cervical endocoil is specially designed to slip over the cervix to give very high in-plane resolution. Tumour volumes greater than 2 mm^3 may be recognized. There are some beautiful illustrations of very small cancers that argue strongly for the value of endocavitary imaging for early cervical cancer. The use of endocoils in both prostate and rectal cancer is less conclusive. Perhaps both reflect the problems with endorectal balloon coil design. Imaging of the female urethra is described using a 7-mm diameter endocoil, but there is little evidence for the clinical value of this. The editor's work in endocoil imaging of the anal sphincter is well known, and this technique is particularly useful to demonstrate external sphincter atrophy and to assess residual sphincter anatomy in congenital anomalies.

The pace of technical development in radiology seems relentless, and what was thought impossible a few years ago is now routine. In magnetic resonography, gradients have increased dramatically such that tissue warming and muscle twitching may be induced, and external coils are continually refined. This has not made endocoils obsolete, but does mean there is now less difference in resolution between endocoils on an old magnet and exocoils on a new one. Of course, endocoils on a new magnet may take us another stage further in anatomical resolution. This book is, therefore, a snapshot in a period of a rapidly evolving technology. It is well written, informative and the illustrations are of good quality. Unfortunately many of these coils are not available from the larger manufacturers. It may be a few years before the clinical role of endocoils becomes clearer and their place either more widely accepted or rejected. These factors limit the general interest of this book, as the use of endocavitary coils still remains largely the province of research units.

C. Bartram
Department of Intestinal Imaging
St Mark's Hospital
Northwick Park
Harrow HA1 3UJ
UK

Pathology and Immunology of Transplantation and Rejection

S. Thiru and H. Waltmann

252 × 191 mm. Pp. 583. Illustrated. 2001. Oxford: Blackwell Science. £125·00.

The knowledge and results of solid organ transplantation both expand every year. Operative morbidity and mortality rates decrease as a result of newly introduced surgical techniques and immunosuppressive drugs. Short-term results are likely to improve as more experience is gained with the addition of interleukin 2 receptor blockers to the standard therapy with calcineurin inhibitors. It is hoped that the decrease in the number of rejection episodes will outweigh any possible increase in infectious complications. The role of corticosteroids, especially for long-term prevention of rejection, is under debate. It is with this background that this extensive and impressive book should be regarded. In this fast moving field it is a daring enterprise to give a full account of current knowledge at a specific moment and the authors are to be congratulated on a superb achievement. The first five chapters describe in a clear and concise manner the genetics and molecular biology of histocompatibility, immunosuppression and rejection, with special emphasis on links to the clinical setting and recent developments. Simple illustrations add to the comprehensiveness of the text. Immunobiology and histocompatibility are discussed in the light of the latest developments and, especially informative for the clinician, are the chapters about new methods in tissue typing and the enigma of the blood transfusion effect. Clinical immunosuppression in renal transplantation is extensively discussed but specific aspects of immunosuppression in liver, heart, lung and pancreas transplantation receive less attention. Much essential and recent information is given in the respective chapters about early and late viral, bacterial, fungal and parasitic infections after abdominal and thoracic organ transplantation. The difficulties in diagnosis, pathology and management after transplantation are set out clearly and informatively. The book contains an extensive and practical index. As pathology is the main interest of both editors, it is not surprising that this important volume makes a fully justified plea for close collaboration between the different specialties in order to improve further the early and late results of solid organ transplantation.

H. W. Tilanus
Department of Surgery
Liver Transplant Unit
Erasmus University Medical Centre
Rotterdam
The Netherlands

Textbook of Surgery. 2nd ed.

J. J. Tjandra, G. J. A. Clunie and R. J. S. Thomas (eds)
249 × 174 mm Pp 717 Illustrated 2001. Melbourne Blackwell Science Asia £29·50

This is an Australasian textbook of surgery aimed at medical students and postgraduate trainees. It provides more than adequate information for the medical student and, although it is a good introduction to surgery for the surgical trainee, it is not advanced enough for the Membership of the Royal College of Surgeons examination. The book is well presented as a glossy-covered paperback with good quality paper and clear print. The text is well laid out with clear subheadings and is amply illustrated with tables and figures, photographs and radiological images. Boxes are used to summarize important points covered in the text, such as differential diagnosis, investigation pathway and management of the condition being discussed. The tables and boxes are printed in pale blue and with the figures are simple and easy to interpret. The volume is fairly comprehensive covering the principles of surgery (97 pages), most topics in general surgery and one or two chapters on each of the other surgical specialties. It finishes with 70 pages of chapters on problem solving where the reader is taken through the diagnostic and management process of a specific clinical presentation such as haematemesis and melaena, the acute abdomen, neck swelling, leg ulcers and postoperative complications. This is a useful section as it helps the reader learn how to make a diagnosis and manage patients, and apply the knowledge gained about individual conditions. The text is up-to-date, concise and clearly written in simple language that is easy to understand.

S. Cheslyn-Curtis
Luton and Dunstable Hospital
Lewsey Road
Luton LU4 0DZ
UK

Minimally invasive cancer management

F. L. Greene and B. T. Heniford (eds)
258 × 180 mm Pp 385 Illustrated 2001 New York Springer. £89 50.

This is a well produced and comprehensive text outlining aspects of minimally invasive cancer management. It covers the general oncological principles behind cancer treatment and considers the pros and cons of cancer management in this way. There are chapters on ultrasonographic techniques in minimal access surgery and the authors also discuss organ-specific areas of treatment in the abdomen, thorax and retroperitoneum. In addition specialized issues such as minimal access cancer management in children and sentinel lymph node biopsy are addressed. Each chapter is written by experts in the field and is well illustrated and referenced. The comprehensive nature of the book is such that it will appeal to those from various subspecialties who have an interest in laparoscopic oncological surgery.

J. Beynon
Department of Colorectal Surgery
Singleton Hospital
Sketty
Swansea SA2 8QA
UK

Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Brown SR, Ballan K, Ho E, Ho YH, Fams F, Seow-Choen F. Stapled mucosectomy for acute thrombosed circumferentially prolapsed piles: a prospective randomized comparison with conventional haemorrhoidectomy. *Colorectal Disease* 2001; **3:** 175–8.

Thirty-five consecutive patients were studied. Pain scores were higher for the stapled group at discharge, but then lower in this group after 2 weeks. The rate of persistent symptoms was higher after conventional surgery at 2 and 6 weeks. Return to work was quicker after the stapled operation (14 *versus* 28 days, $P < 0.05$).

Lindgren PG, Nordgren SR, Öresland T, Hulten L. Midline or transverse abdominal incision for right-sided colon cancer – a randomized trial. *Colorectal Disease* 2001; **3:** 46–50.

The transverse incision reduced postoperative pain on exertion and improved pulmonary function in this study of 40 operations.

Thomas S, Agarwal M, Mehta G. Intraoperative glove perforation – single *versus* double gloving in protection against skin contamination. *Postgrad Medical J* 2001; **77:** 458–60.

Double gloving reduced skin contamination from 42 to 23 per cent in the 66 procedures studied. On 82 per cent of occasions when the outer glove was perforated, the inner glove protected the surgeon's skin.

Rucinski J, Margolis M, Panagopoulos G, Wise L. Closure of the abdominal midline fascia: meta-analysis delineates the optimal technique. *Am Surg* 2001; **67:** 421–6.

Data from this review of randomized trials from the last 20 years suggested that the optimal technique was all layer closure with absorbable monofilament suture material.

CAVATAS Investigators. Endovascular *versus* surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001; **357:** 1729–37.

Rates of disabling stroke and death were similar for surgery (5·9 per cent) and angioplasty (6·4 per cent) in this trial including 504 patients. Some 9 per cent of surgery patients had a cranial neuropathy. Survival rates were similar at 3 years.

Sarli L, Villa F, Marchesi F. Hernioplasty and simultaneous laparoscopic cholecystectomy: a prospective randomized study of open tension-free *versus* laparoscopic inguinal hernia repair. *Surgery* 2001; **129:** 530–6.

Some 64 patients were included; laparoscopic hernia repair took longer and was more expensive, but it reduced the intensity of postoperative pain though it did not affect the duration of recovery.

Frank JL, Garb JL, Halla B, Reed WP Jr. Ionic implantation of silicone chronic venous access devices does not alter thrombotic complications: a double-blinded randomized clinical trial. *Surgery* 2001; **129:** 547–51.

One hundred patients who needed chemotherapy were included. The incidence of occlusion on aspiration was not reduced when ionic implantation catheters were used compared to standard catheters (47 *versus* 39 per cent, P = not significant).

Werre AJ, Palamba HW, Bilgen EJ, Eggink WF. Isosorbide dinitrate in the treatment of anal fissure: a randomized, prospective, double blind, placebo-controlled trial. *Eur J Surg* 2001; **167:** 32–5.

Some 17 of 20 patients treated with isosorbide compared with 6 of 17 controls were healed after 5 weeks ($P < 0.003$). Two fissures recurred in each group.

Fisher B, Dignam J, Bryant J, Wolmark N. Five *versus* more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst* 2001; **93:** 684–90.

This was an update of 1172 patients randomized to continue tamoxifen or placebo 5 years after breast cancer surgery. Overall survival rates were 94 per cent in controls *versus* 91 per cent with tamoxifen and disease-free survival rates were 82 and 78 per cent, respectively ($P = 0.03$).

Khan S, Pawlak SE, Eggenberger JC, Lee CS, Szilagy EJ. Prospective randomized trial comparing closed exisional haemorrhoidectomy and the harmonic scalpel technique of excisional haemorrhoidectomy. *Dis Colon Rectum* 2001; **44:** 845–9.

The duration of surgery, amount of postoperative pain and recovery rate were similar in this trial including 30 patients.

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Instructions to authors

BJS publishes original articles, reviews and leading articles all of which are submitted to peer review.

An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap. Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Send four copies of original articles and other editorial matter to: The Editor, *BJS*, Blackwell Science Ltd, 25 John Street, London WC1N 2BS, UK. Telephone: 0207 404 1831; facsimile: 0207 404 1927. A version on disk must accompany all submitted material. For instructions on how to do this, see below Books for review should be sent to the same address.

A covering letter must accompany all submissions, must be signed by all authors and must state whether an abstract of the work has been published - please provide an appropriate reference. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The Journal takes very seriously its obligation to assess and declare any actual or potential conflicts of interest. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support. The first named author is responsible for ensuring that all authors have seen, approved and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; 308 39–42) and the COPE guidelines on good publication practice (www.publicationethics.org.uk). If a paper has more than six authors you must justify the inclusion of all names Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; 345: 668). The Editors are of the view that those with a peripheral association with the work should simply be acknowledged (*BJS* 2000; 87: 1284–6).

Disks

IBM-compatible disks would be preferred (3½ inch) An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors. Proofs will be sent via e-mail as an Acrobat portable document format (PDF) file.

Rejected manuscripts and illustrations will not normally be returned.

Ethics

Material relating to human investigation and animal experiments must comply with and be approved by local ethics committees It must conform to standards currently applied in the country of origin. The Journal reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication of any details or photographs that might identify an individual Submit evidence of such consent with the manuscript.

Preparation of manuscripts

BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; 336: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy)

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation **Randomized clinical trials** should be clearly identified as such in the title and abstract.

Reviews and meta-analyses of randomized trials

The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; 354: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance The Editors retain the right to alter style and shorten material for publication An honorarium is payable on publication

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal Responses can be sent

electronically via the *BJS* website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (www.consort-statement.org).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:[1] or [1–3]. References cited only in tables or figures should be numbered in sequence.

British Journal of Surgery

The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Society of Academic and Research Surgeons, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

Editorial Team

Editors
J. A. Murie, *Edinburgh, UK*
J. R. Farndon, *Bristol, UK*

Associate Editors
P. J. Guillou, *Leeds, UK*
P. R. O'Connell, *Dublin, Ireland*

Website Editor
J. J. Earnshaw, *Gloucester, UK*

Statistical Consultant
G. D. Murray, *Edinburgh, UK*

Council

Chairman
R. C. G. Russell, *London, UK*

Vice-Chairman
T. Bates, *Ashford, UK*

Treasurer
N. J. McC. Mortensen, *Oxford, UK*

Company Secretary
J. R. C. Sainsbury, *London, UK*

D. Alderson, *Bristol, UK*
J. Bancewicz, *Salford, UK*
M. Büchler, *Berne, Switzerland*
V. W. Fazio, *Cleveland, Ohio, USA*
K. C. H. Fearon, *Edinburgh, UK*
I. G. Finlay, *Glasgow, UK*
(Royal College of Surgeons)
P. Lamont, *Bristol, UK*
(Society of Academic and Research Surgeons)
M. Lee, *Birmingham, UK*
(Association of Surgeons)
J. P. Neoptolemos, *Liverpool, UK*
H. Obertop, *Amsterdam, The Netherlands*
M. Rothmund, *Marburg, Germany*
C. J. H. van de Velde, *Leiden, The Netherlands*

Editorial Board

W. H. Allum, *UK*
C. Bassi, *Italy*
J. Beynon, *UK*
N. J. Bundred, *UK*
W. B. Campbell, *UK*
F. Castro-Sousa, *Portugal*
S. C. S. Chung, *Hong Kong*
J. D. Corson, *USA*
D. Demetriades, *USA*
D. M. Dent, *South Africa*
C. Dervenis, *Greece*
T. Diamond, *UK*
L. Fernández-Cruz, *Spain*
A. Fingerhut, *France*
O. J. Garden, *UK*
D. Gotley, *Australia*
D. J. Gouma, *The Netherlands*
P. A. Grace, *Ireland*
U. Haglund, *Sweden*
M. Kitajima, *Japan*
Z. H. Krukowski, *UK*
G. J. Maddern, *Australia*
N. Nagasue, *Japan*
A. R. Naylor, *UK*
S. Nicholson, *UK*
B. Nordlinger, *France*
L. Påhlman, *Sweden*
A. L. G. Peel, *UK*
F. Penninckx, *Belgium*
L. F. Rikkers, *USA*
B. J. Rowlands, *UK*
S. Rudzki, *Poland*
F. Seow-Choen, *Singapore*
A. Sitges-Serra, *Spain*
O. Soreide, *Norway*
R. A. J. Spence, *UK*
M. D. Stringer, *UK*
K. Sugimachi, *Japan*
J. M. Thomas, *UK*
S. Vittal, *India*
T. N. Walsh, *Ireland*
A. L. Warshaw, *USA*
S. D. Wexner, *USA*
M. H. Wheeler, *UK*

Calcutta University College of Medicine
LIBRARY

While every effort is made by the Editorial Team, members of Council and the publishers to avoid inaccurate or misleading information appearing in *BJS*, data within the individual articles and advertisements are the responsibility of the authors or advertisers concerned. The BJS Society, the publishers, and members of the Editorial Team and Council accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

The *BJS* ISSN 0007-1323

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *BJS*, Blackwell Science Ltd,
25 John Street, London WC1N 2BS, UK (Tel: +44 0207 404 1831).

Manager	Elizabeth Whelan
Production Editor	Emma Missen (emma.missen@blacksci.co.uk)
Editorial Assistant	Mary Savigar

Aims and scope

BJS is the premier general surgical journal in Europe and one of the top surgical periodicals in the world. Its international readership is reflected in the prestigious international Editorial Board, supported by a panel of over 1200 reviewers worldwide.

BJS features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented.

The inclusion of Leading Articles, Reviews and Original Articles means that *BJS* offers an appropriate format for any length or type of submission; in addition, there are abstracts from key meetings, correspondence and book reviews. *BJS* will be of interest not only to general surgeons, but also to specialty surgeons and those working in related fields.

Subscriptions

BJS is published monthly (one volume per annum) in 2001. Print subscription prices for 2001 are:

	EUROPE	REST OF WORLD	NORTH AMERICA
Institutional	£146.00	£169.00	$261.00
Individual	£87.00	£101.00	$156.00
All Trainee Surgeons UK and ASIT			
	£43.50	£50.50	$78.50
Surgeons in Training Worldwide			
	£43.50	£50.50	$78.50

For online access in addition to print, please add 10 per cent to the print subscription price. For an online subscription without a print subscription, please pay 90 per cent of the print subscription price.

All members of the Association of Surgeons of Great Britain and Ireland, Surgical Research Society and Association of Surgeons of the Netherlands receive the paper journal as a benefit of membership of the society. In addition, all members have full access to the online version of the journal.

Subscribers in Canada must add 7% to the subscription price to allow for GST. Subscribers in Europe must quote their VAT registration number or state that they are not registered. Subscribers in the following countries who are not VAT-registered must add VAT at the appropriate rate:

Belgium (6% TVA/BTW)
France (2.1% TVA)
Germany (7% MWST)
Spain (4% IVA)
The Netherlands (6% BTW)

Orders for current subscriptions and back issues should be sent to Blackwell Science Ltd, Journal Subscriptions, PO Box 88, Oxford OX2 0NE, UK. Tel: +44 1865 206180; Fax: +44 1865 206219; e-mail: jnl.orders@blacksci.co.uk

Despatch

BJS is despatched within the UK by second class post, within Europe by air mail, and to other continents by various forms of air-speeded delivery, to the USA by air freight for forwarding by second class post*, to India by air freight for guaranteed local delivery, and to all other countries by accelerated surface post. Add to the cost of a regular subscription £24.00/$36.00 for air mail delivery outside Europe.

Business correspondence

All other business correspondence, including orders for offprints (offprints@blacksci.co.uk) and advertising space (advert@blacksci.co.uk) should be addressed to:
BJS, Blackwell Science Ltd, Osney Mead,
Oxford OX2 0EL, UK. (Tel. +44 1865 206206;
Fax: +44 1865 721205).

Copyright and photocopying

© 2001 Blackwell Science, acting as agents for the BJS Society.
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Science for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $15 per copy is paid directly to CCC, 222 Rosewood Drive, Suite 910, Danvers, MA 01973, USA. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to the publisher.

Paper

The Publisher's policy is to use acid-free permanent paper, to the draft standard ISO/DIS/9706, made from sustainable forests using chlorine-free pulp. The paper used in this journal has an ECO-CHECK 4-star rating.

BJS has a worldwide website at: http://www.bjs.co.uk

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the publisher.

Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

UNIVERSITY OF DUNDEE

SURGICAL SKILLS UNIT

The Surgical Skills Unit provides high quality skills training aimed at improving surgical competence and execution related to particular specialties. The training covers predominantly, but not exclusively, endoscopic skills at three levels: basic, advanced and procedure related.

A variety of courses are regularly available:

- **Essentials of Laparoscopic Surgery**
- **Advanced Endoscopic Surgery Skills**
- **Gynaecology**
- **Otolaryngology**
- **Anaesthetics**
- **Paediatrics**

Other specialist courses are held according to demand. Please contact us with your requirements.

Details of the Unit and all of our courses are available at:

www.dundee.ac.uk/surgicalskills

MINIMAL ACCESS THERAPY TRAINING UNIT SCOTLAND

Contact: Mrs A Duncan
Surgical Skills Unit
Level 5, Ninewells Hospital and Medical School,
Dundee, DD1 9SY
Tel. 01382 645857 Fax 01382 646042

North Shore University Hospital-Long Island Jewish Health System
Long Island, New York

Seeking Several Registrars in Surgery

Qualified individuals will serve for one to two years, beginning July 2002, at Huntington Hospital, a level II trauma center, and affiliate of the North Shore -LIJ Health System. These are not American Board of Surgery residency positions, but are positions as surgical fellows in association with the North Shore-LIJ Surgical Residency program.

Successful applicants will be proficient in English, have passed all examinations necessary to work in the United States, and be qualified to supervise first year surgical residents.

Interested individuals should forward their Curriculum Vitae, and 3 letters of recommendation to:

Dr. David Benisch, Director of Surgical Residency,
Huntington Hospital, 270 Park Avenue, Huntington, New York 11743, United States
Tel. 631-351-2609 / Fax. 631-351-2795 / Email: cnehl@hunthosp.org

Huntington Hospital and the North Shore-LIJ Health system are Equal Opportunity Employers, and encourage applicants of every gender, creed, race and national origin

HUNTINGTON HOSPITAL
LIJ
NORTH SHORE - LONG ISLAND JEWISH HEALTH SYSTEM

MONOCRYL

(poliglecaprone 25) suture

A technological innovation among synthetic absorbable sutures. Unprecedented monofilament pliabilit and smooth passage through tissue.

ETHICON
a Johnson & Johnson company
ETHICON Limited, PO Box 408, Bankhead Avenue, Edinburgh,
EH11 4HE, United Kingdom.

For further information please contact your loca
ETHICON representative,
call our Customer Services on 0800 864 060,
or visit us at www.jnjgateway.com
Capitalised product names are trademarks of ETHIC

Contents

British Journal of Surgery

Volume 88, Issue 11, November 2001

Leading articles

1425 **Irritable bowel syndrome: new horizons in pathophysiology and treatment**
M. Bose and M. J. G. Farthing
An individually tailored combination of therapies is advocated

1427 **Present and future management of deep vein thrombosis**
B. D. Braithwaite
New drugs and new protocols

Reviews

1429 **Molecular mechanisms of renal allograft fibrosis**
J. R. Waller and M. L. Nicholson
The leading cause of graft loss after the first year following transplantation is discussed

1442 **Management of thoracic duct injuries after oesophagectomy**
S. A. Wemyss-Holden, B. Launois and G. J. Maddern
The thoracic duct should be ligated during oesophagectomy

Randomized trials

1449 **Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy**
Y.-H. Ho, F. Seow-Choen, C. Tsang and K.-W. Eu
Use of a dilator increases the risk of sphincter damage after stapled haemorrhoidectomy

1456 **Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy**
C. Gouillat, J. Chipponi, J. Baulieux, C. Partensky, J. Saric and B. Gayet
Somatostatin reduced pancreatic stump-related complications

Original articles

1463 **Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma**
M. Shimada, Y. Yamashita, S. Aishima, K. Shirabe, K. Takenaka and K. Sugimachi
No advantage seen for extended lymphadenectomy

1467 **Readmissions after pancreatoduodenectomy**
R. C. I. van Geenen, T. M. van Gulik, O. R. C. Busch, L. T. de Wit, H. Obertop and D. J. Gouma
Prognosis is poor if readmission is for reoperation for recurrence

1472 **Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms**
J. S. Lindholt, E. J. Erlandsen and E. W. Henneberg
No clinical application, but further insight into the cause of aneurysms

1476 **Methodology and reporting in studies of local recurrence after curative excision of the rectum for cancer**
O. F. Dent, P. H. Chapuis, E. L. Bokey and R. C. Newland
Correct methodology vital

1481 **Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence**
D. F. Altomare, G. Dodi, F. La Torre, G. Romano, E. Melega and M. Rinaldi
Encouraging results with artificial anal sphincter

TO ADVERTISE IN THIS JOURNAL CONTACT:

Katrina Erskine

☎ : + 44 (0) 1865 206238 or
Fax: +44 (0) 1865 206189
Email katrina.erskine@blacksci.co.uk

Or access our website for further information:
http://www.blackwell-science.com

Blackwell
Science

Blackwell Science Ltd, Osney Mead, Oxford, OX2 0EL, UK

Royal Society of Medicine Award Winner
"Telemedicine and Telecare in the NHS, 2000"

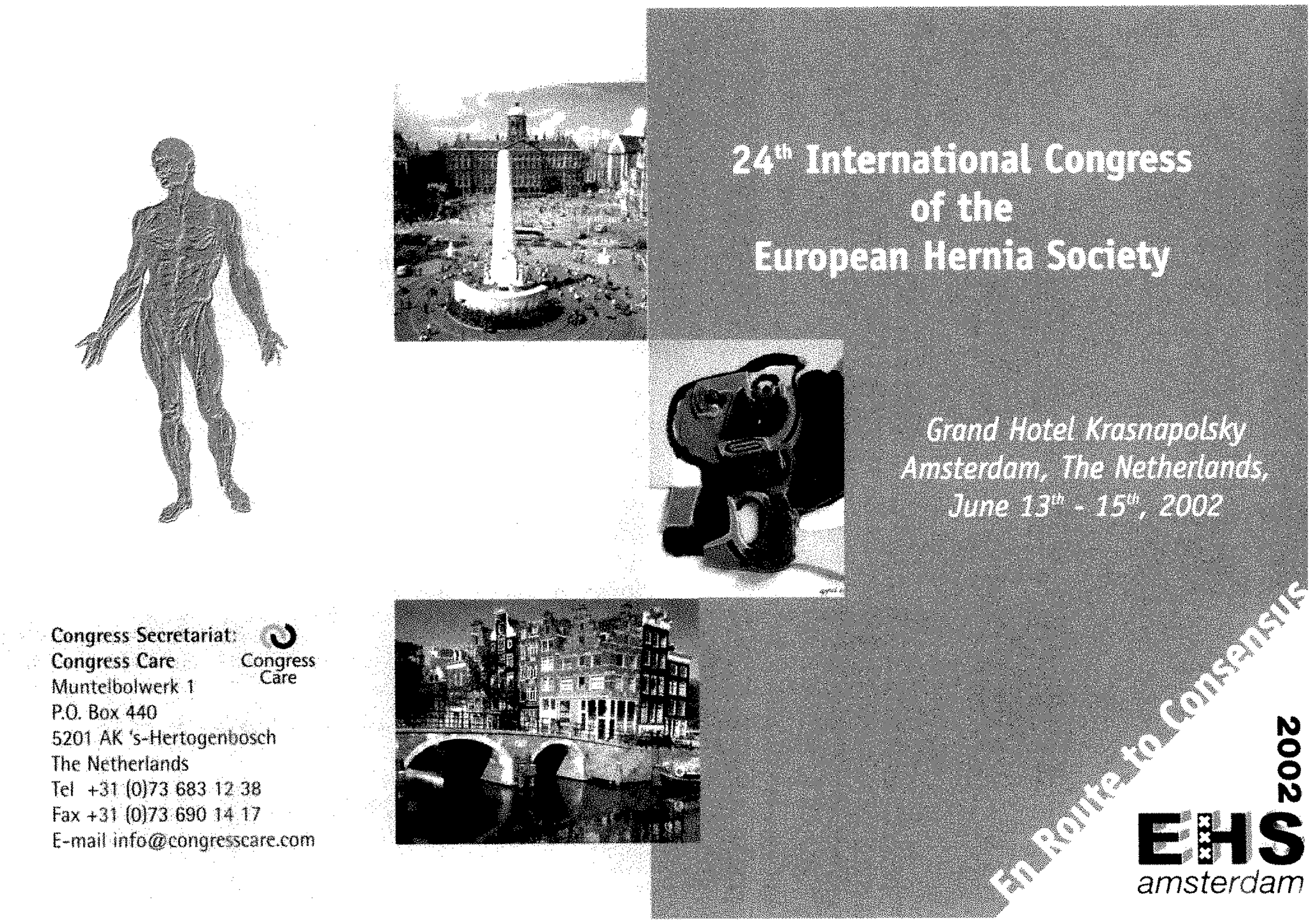
Surgical Training via Digital Satellite TV
Free broadcasts to eligible sites for 2001/0

mrcsTV is a novel education and training programme f doctors studying for the examinations at any of the four Roy Colleges of Surgeons in England, Scotland and Ireland. Devise by Professor Andrew Kingsnorth FRCS, FACS and Surgec Commander James Campbell FRCSEd, FRCS, **mrcsTV** also relevant to doctors studying for similar qualifications arour the world.

A series of 30 live TV programmes, each of 90 minutes duratio is broadcast on Friday lunchtimes from the University Plymouth via high quality digital satellite TV to suitably equippe hospital education centres across the UK and Eire. Thes broadcasts cover a range of topics in modular format releva to the MRCS syllabuses produced by the Royal Colleges.

- *learning in the workplace - saves travel time*
- *learning in the workplace - saves travel costs*
- *wider access to expert presenters*
- *opportunity to ask the experts questions*
- *access to video and photograhic content*
- *interaction with other surgical trainees*

For more information on how your hospital can connect to the **mrcsTV** network, call Tracey Honeychurch on 01752 763017 or e-mail her at: **tracey.honeychurch@phnt.swest.nhs.uk** or look at our web site **http://www.mrcs.tv**



24th International Congress of the European Hernia Society

Grand Hotel Krasnapolsky
Amsterdam, The Netherlands,
June 13th - 15th, 2002

Congress Secretariat:
Congress Care
Muntelbolwerk 1
P.O. Box 440
5201 AK 's-Hertogenbosch
The Netherlands
Tel +31 (0)73 683 12 38
Fax +31 (0)73 690 14 17
E-mail info@congresscare.com

1487 **Long-term effects of stapled haemorrhoidectomy on internal anal function and sensitivity**
D. F. Altomare, M. Rinaldi, P. L. Sallustio, P. Martino, M. De Fazio and V. Memeo
Function and sensitivity are preserved

1492 **Ileoanal pouch function is related to postprandial pouch tone**
J. Steens, W. A. Bemelman, W. J. H. J. Meijerink, G. Griffioen, R. A. van Hogezand and A. A. M. Masclee
Ileal pouch function investigated

1498 **Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative**
L. Basse, J. L. Madsen and H. Kehlet
Transit is normal after 48 h

1501 **Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery**
C. A. Maurer, K. Z'graggen, P. Renzulli, M. K. Schilling, P. Netzer and M. W. Büchler
Total mesorectal excision preserves sexual function to a greater extent than conventional rectal excision

1506 **Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging**
G. L. Morren, R. G. H. Beets-Tan and J. M. A. van Engelshoven
New technique to define anatomy of the anal canal

1513 **Estimating the benefits of adjuvant systemic therapy for women with early breast cancer**
M. Grogan, L. Tabar, B. Chua, H.-H. Chen and J. Boyages
Useful data for breast surgeons and their patients

1519 **Prospective study of the effect of laparoscopic Nissen fundoplication on reflux mechanisms**
J. W. A. Straathof, J. Ringers and A. A. M. Masclee
Fundoplication reduces the rate of transient lower oesophageal sphincter relaxation and preserves postprandial characteristics

1525 **Validity of surgical simulation for the assessment of operative skill**
A. M. Paisley, the late P. J. Baldwin and S. Paterson-Brown
Existing tests are not yet very reliable

1533 **'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery**
C. P. Delaney, V. W. Fazio, A. J. Senagore, B. Robinson, A. L. Halverson and F. H. Remzi
'Fast track' protocol is safe and enables rapid recovery and early discharge

1539 **Conservative management of appendix mass in children**
J. Gillick, M. Velayudham and P. Puri
A study including over 400 children

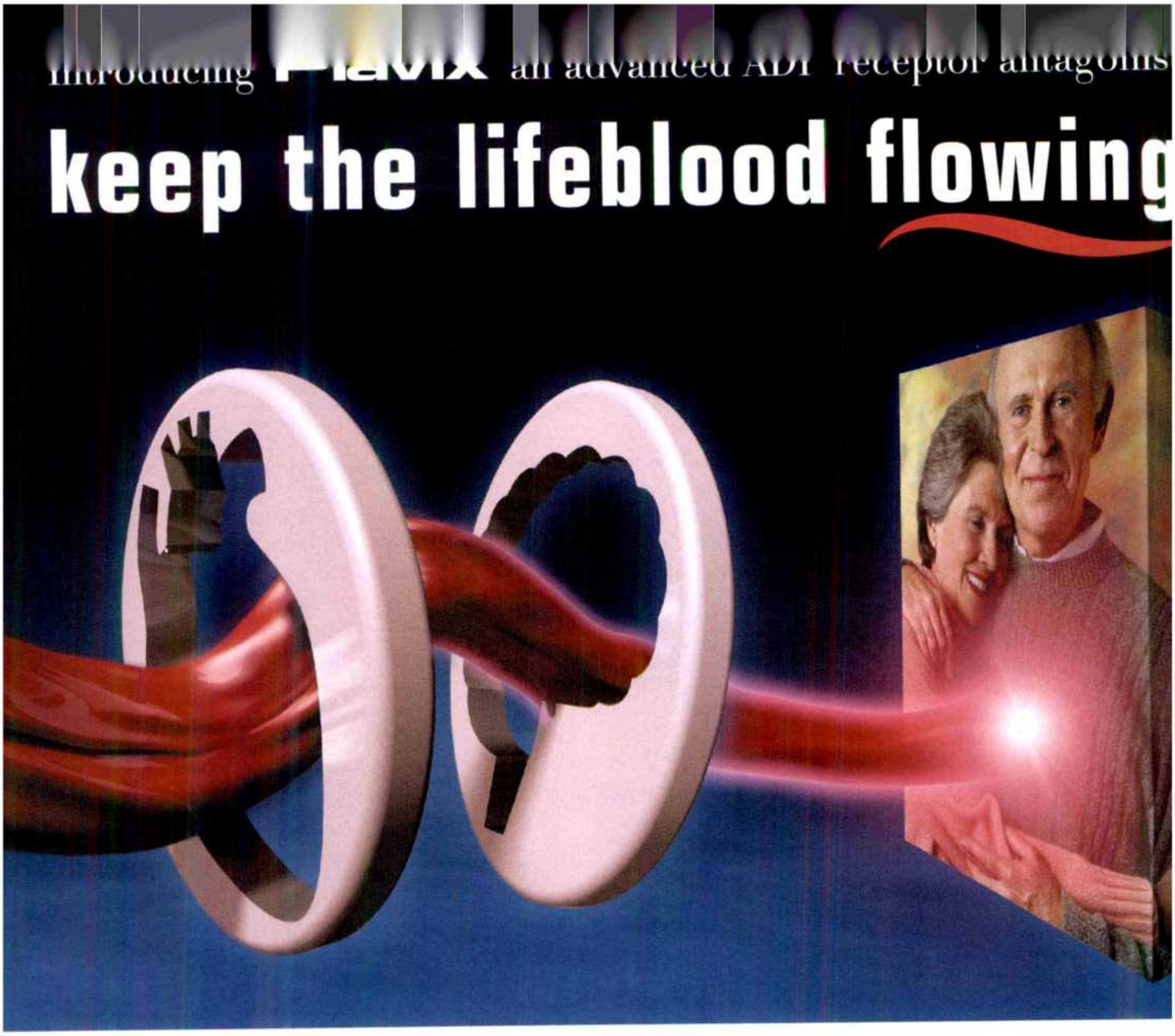
1543 **Correspondence**

1549 **Book reviews**

1550 **Scientific surgery**

1551 **Instructions to authors**

0007-1323(200111)88:11;1-C


Introducing Plavix an advanced ADP receptor antagonis
keep the lifeblood flowing

Introducing PLAVIX - the first drug specifically designed for, and proven in, the prevention of further ischaemic events: MI, STROKE and VASCULAR DEATH.*

In a trial against aspirin in over 19,000 recent MI, recent ischaemic stroke and atherosclerotic PVD patients, PLAVIX was proven to be significantly more effective at reducing further events: MI, STROKE and VASCULAR DEATH.[1]*

PLAVIX PRESCRIBING INFORMATION. PRESENTATION: Round, pink, film coated tablets containing 75mg clopidogrel (as the bisulphate). INDICATION: Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days), or established peripheral arterial disease. DOSAGE: Adults and elderly: 75mg as a single daily dose. Children and adolescents: Not recommended under 18 years. CONTRAINDICATIONS: Hypersensitivity to clopidogrel or excipients; severe liver impairment; active pathological bleeding; breast-feeding. WARNINGS: Due to the risk of bleeding and haematological disorders, blood cell count determination should be conducted where suspected clinical symptoms arise during treatment; caution in patients with lesions likely to bleed, particularly gastrointestinal and intraocular; renal impairment; hepatic disease. Not recommended during pregnancy. DRUG INTERACTIONS: Not recommended with warfarin. Caution when used with acetylsalicyclic acid, NSAIDS, heparin, thrombolytics, glycoprotein IIb/IIIa inhibitors. Blood cell count determination is required during first week of co-administration. SIDE EFFECTS: Haematological

*CAPRIE: comparison of efficacy of clopidogrel versus aspirin; Inclusion criteria patients with ischaemic stroke (from 7 days to less than 6 months), MI (less tha days) or established peripheral vascular disease; Endpoint: Combined endpoin MI, ischaemic stroke, vascular death for the overall population

Plavix

clopidogrel 75mg

PREVENTING VASCULAR EVENT

sanofi~synthelabo Bristol-Myers Squ

disorders including very rare cases of thrombotic thrombocytopenic purpura, very rare c of severe thrombocytopenia, agranulocytosis, anaemia and aplastic anaemia / pancytop haemorrhagic including serious bleeding such as skin bleeding, bruising, haemarthrosis, haemat eye bleeding, epistaxis, respiratory tract bleeding, haematuria and intracranial, gastrointestina retroperitoneal haemorrhage and haemorrhage of operative wound; gastrointestinal incl diarrhoea; very rare cases of renal disorders and abnormal creatinine levels; allergic diso including skin reactions, bronchospasm, angioedema, anaphylactoid reactions, fever, arthralgi arthritis; very rare cases of taste disorders and confusion. LEGAL CATEGORY: POM. PRO LICENCE NUMBER: EU/1/98/069/001a. MARKETING AUTHORISATION HOLDER: Sanofi Ph Bristol-Myers Squibb SNC. FURTHER INFORMATION IS AVAILABLE FROM: Sanofi-Synth One Onslow Street, Guildford, Surrey, GU1 4YS. TEL: 01483 505515. FAX: 01483 53 BASIC NHS PRICE: £35.31 for 28 tablets. DATE OF PREPARATION: September Reference: 1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel v aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1

PLA 01/183

Leading article

Irritable bowel syndrome: new horizons in pathophysiology and treatment

M. Bose and M. J. G. Farthing*

Department of Paediatric and Adult Gastroenterology, St Bartholomew's and The Royal London School of Medicine and Dentistry, Turner Street, London E1 2AD (e-mail: M.Bose@mds.qmw.ac.uk) and *Faculty of Medicine, University of Glasgow, Southpark Terrace, Glasgow G12 8LG, UK (e-mail: m.farthing@clinmed.gla.ac.uk)

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder in the Western world, which affects about 10–20 per cent of the general population with a male : female ratio of 1 : 2. It is defined as a disorder in which abdominal discomfort or pain is associated with defaecation or a change in bowel habit, and with features of disordered defaecation. The diagnosis is subcategorized according to the Rome Criteria[1]. Routine investigation reveals no evidence of structural or biochemical abnormality. IBS is responsible for a large number of primary care consultations and subsequent referrals to hospital gastroenterology services. As a chronic condition that affects otherwise fit members of the productive age group, it reduces quality of life and results in lost working hours. Based on data from 1995, one group found that the annual expenditure on IBS by the UK National Health Service was about £46 million. Most importantly, because of its traditional position as a diagnosis of exclusion, it has come to have negative connotations for both patients and clinicians. For these reasons, along with the possibility of effective treatment for the condition, there has been an active search for the pathophysiological mechanisms that produce the symptoms of IBS.

Initial attention focused on possible abnormalities of intestinal motility. Manometry was used to characterize a variety of abnormalities of colonic motility, including an enhanced response to stress and food. Abnormalities in small intestinal motility have also been reported[2], but there is no consistent pattern and so motility dysfunction alone cannot account for all the presenting features of IBS. More recently there has been increased interest in visceral sensation and the processing of noxious and non-noxious stimuli. Barostat or balloon distension models have been used to assess intestinal wall compliance and relate this to visceral hypersensitivity. These studies appear to confirm increased hypersensitivity in those with IBS compared with healthy controls. Central nervous system imaging techniques have been used to study the central processing of visceral stimuli. Differences in central processing can be shown between patients with IBS and healthy controls[3]. One study showed increased dorsolateral prefrontal cortical blood flow in anticipation of rectal pain[4]. Other work has examined regional brain 5-hydroxytryptamine (5-HT) synthesis rates in male and female patients using positron emission tomography (PET)[5]. PET images were converted to 5-HT synthesis rates by calculating the brain uptake constant for data collected between 20 and 60 min after tracer injection. No significant differences were found between male patients and controls, but female patients had several brain regions in which 5-HT synthesis was higher than that in female controls.

Functional magnetic resonance studies have shown differential processing in the insular cortex, angular cingulate cortex and dorsolateral prefrontal cortex in subjects undergoing rectal distension. Cerebral deactivations were observed in certain areas responsible for the processing of visceral pain and its affective or cognitive components in patients, but not in healthy volunteers[6]. Sham rectal distension has also been examined to assess the effect of anticipation on brain activation. Psychological variables and expectation play an important role in brain activation during rectal pain but do not appear to account for the increased activation in IBS compared with controls in the anterior cingulate gyrus[7]. Another developing concept is that of central sensitization or 'wind-up' in which repeated electrophysiological peripheral stimulation leads to persistent hypersensitivity of spinal afferents[8].

Gastrointestinal infection has also been implicated in the pathophysiology of IBS. Studies have shown that 25 per cent of patients who present with IBS can relate the start of their symptoms to a previous episode of infective diarrhoea[9]. It is postulated that changes in mucosal inflammation associated with acute infection might induce chronic visceral hypersensitivity by inducing neuroplastic changes in visceral afferent pathways. Sensitized immune cells might later be activated by psychological stress, or possibly act by inducing a chronic low-grade or preinflammatory state which then acts on visceral afferents in a chronic manner[3]. Mast cells and lymphocytes have been found in closer proximity to nerve trunks in patients with IBS than in controls, together with increased numbers of degranulated mast cells and ultrastructural neural alterations[10]. Whorwell's group performed a study that examined differences in interleukin 10 and transforming growth factor genotypes between patients and controls; the low producer allele appeared to be linked to IBS[11].

The above features have led to recognition of the importance of the role of both central and peripheral components in the pathogenesis of IBS. The result has been the development of the concept of the brain–gut axis. In this model it is proposed that the brain and the enteric nervous system of the gut act together to modulate behaviour that leads to presentation with IBS. The putative importance of the neurohumoral elements of the brain–gut axis in IBS has led to interest in the various neurotransmitters that are involved in signal transduction in this system. A treatment approach consistent with concepts of brain–gut dysfunction is likely to involve neuropeptides and their receptors present in both the enteric and central nervous systems. Putative agents include 5-HT, the enkephalins and opioid agonists, substance P, calcitonin gene-related polypeptide and cholecystokinin.

Modes of therapy for IBS are aimed at breaking cycles within the brain–gut axis. Successful interventions with central action, including hypnotherapy, behavioural therapy, relaxation therapies, biofeedback and treatment with antidepressants, have been reported. Previous studies of the role of 5-HT in IBS have relied predominantly on the use of 5-HT receptor antagonists and this has led to the development of agents that act on a variety of 5-HT receptors. The 5-HT$_3$ receptor antagonist alosetron has been shown to reduce symptoms in women with diarrhoea-predominant IBS but it was not effective in men. Soon after launch alosetron was withdrawn in the USA by the Food and Drug Administration because of a series of cases of ischaemic colitis; IBS is not a life-threatening disorder and the risks of any new drug must be weighed against benefit. Other drugs that modulate or mimic the effects of 5-HT are under development for the treatment of IBS.

Tailoring treatment to an individual patient using a combination of therapies is leading to improvement in outcome. In the final analysis, however, one may have to accept that, even with a better understanding of the pathophysiology of IBS and these newer therapies, there will always be some patients with refractory symptoms who are difficult to help.

References

1 Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE. Rome II: a multinational consensus document on functional gastrointestinal disorders. *Gut* 1999; **45**(Suppl II): 1–81.

2 Gorard DA, Farthing MJG. Intestinal motor function in irritable bowel syndrome. *Dig Dis* 1994; **12:** 72–84.

3 Chang L, Munakata J, Mayer EA, Schmulson MJ, Johnson TD, Bernstein CN *et al.* Perceptual responses in patients with inflammatory and functional bowel disease. *Gut* 2000; **47:** 497–505.

4 Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology* 1997; **112:** 2120–37.

5 Diksic M, Nakai A, Kumakura Y, Boivin M, Kersey K. Regional brain serotonin synthesis rates in male and female irritable bowel syndrome (IBS) patients. *Gastroenterology* 2000; **118**(Suppl 2): A80 (Abstract).

6 Bonaz BL, Papillon E, Baciu M, Segebatrh C, Bost R, Le Bas JF *et al.* Central processing of rectal pain in IBS patients: an fMRI study. *Gastroenterology* 2000; **118**(Suppl 2): A615 (Abstract).

7 Mertz HR, Morgan VL, Shyr Y, Pickens DR. The effects of psychologic symptoms and anticipation on cerebral activation during rectal pain in IBS and controls. *Gastroenterology* 2000; **118**(Suppl 2): A844 (Abstract).

8 Sarkar S, Thompson DG, Woolf CJ, Hobson A, Aziz Q. Wind-up in the human viscera: central sensitization contributes to visceral pain. *Gut* 2001; **48**(Suppl 1): A4 (Abstract).

9 Gwee KA, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ *et al.* The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999; **44:** 400–6.

10 Barbara G, Stanghellini V, DeGiorgio R, Pasquinelli G, Cogliandro L, Cenacchi G *et al.* Neuroimmune interactions in the colonic mucosa of irritable bowel syndrome. *Gastroenterology* 2000; **118**(Suppl 2): A138 (Abstract).

11 Chan J, Gonsalkorale WM, Perrey C, Previca V, Hajeer AH, Whorwell PJ *et al.* IL-10 and TGF-β genotypes in irritable bowel syndrome: evidence to support an inflammatory component? *Gastroenterology* 2000; **118**(Suppl 2): A184 (Abstract).

Leading article

Present and future management of deep vein thombosis

B. D. Braithwaite

Department of Vascular Surgery, Queen's Medical Centre, Nottingham NG7 2UH, UK (e-mail lynsdoc@aol.com)

The traditional management of patients with suspected deep vein thrombosis (DVT) requires admission to hospital to allow intravenous infusion of unfractionated heparin. The main aim of this treatment is to prevent thrombus propagation and possible pulmonary embolism. Patients are investigated either by venography or duplex ultrasonography, often performed only during 'office hours'. If a calf DVT is demonstrated warfarin may be prescribed for 3–6 months; if the thrombosis is more extensive warfarin is almost always used. Patients are also advised to wear a graduated compression stocking to reduce the incidence of long-term complications[1].

There are several problems with this strategy. First, only a quarter of those with suspected DVT have the disorder and so three-quarters of admissions are unnecessary, some needlessly exposing patients to several days of hospital-acquired complications before they are fully investigated. Second, confusion still exists about whether calf vein DVT requires anticoagulation[2]. Third, anticoagulation alone does not address the problems of symptom control and secondary deep vein valvular incompetence. In the long term, many patients develop venous hypertension and its complications of oedema and leg ulceration (postphlebitic syndrome).

Structured systems for clinical diagnosis and management of DVT have recently become available so that patients can be treated more appropriately. An important development has been the introduction of subcutaneous fractionated or low molecular weight heparin (LMWH), which has been proven to be as efficacious as standard intravenous heparin in the treatment of DVT[3]. A diagnostic pathway has been developed that scores the likelihood of a patient having a thrombosis as low, moderate or high[4]. The scoring method relies on clinical findings, including carcinoma, immobilization, localized tenderness, oedema and collateral veins; 75 per cent of high-risk, 17 per cent of medium-risk and 3 per cent of low-risk patients may be expected to have a DVT on subsequent investigation[5]. All those with a suspected DVT should have a duplex scan. If normal, those in the low-risk group may be discharged without treatment. Those in the medium-risk group with a normal duplex scan should be rescanned after 1 week as there is a 5 per cent chance of DVT. Only those in the high-risk group with a normal scan and those in the low-risk group with an abnormal scan should have venography. Patients in the low-risk group and, perhaps, those in the medium-risk group with proven DVT should be screened for abnormalities such as Factor V Leiden, and protein C and S deficiencies. Positive findings should prompt advice from a haematologist. This type of structured diagnostic pathway allows an appropriate use of imaging procedures and anticoagulants. If imaging is not readily available, patients at medium or high risk of DVT may be treated with LMWH until a definitive diagnosis can be made. Those at low risk may be discharged to return for investigation within 12–24 h[6].

Most DVTs are confined to the calf, popliteal and superficial femoral veins, and anticoagulation and compression stockings is probably the only management required. A few patients, however, present with extensive iliofemoral venous thrombosis and have a painful swollen leg; they are at high risk of pulmonary embolism. There is some evidence that intravenous thrombolysis or mechanical removal of iliofemoral thrombus can produce rapid symptom relief and restoration of valvular function[7]. Aggressive intervention in such a situation may therefore have a role to play in the prevention of deep venous incompetence and the postphlebitic syndrome.

In some countries an acute medical bed may be difficult to find and in others admission to hospital may be costly. Any change in practice that reduces the need for admission would be welcome. A recent leading article has suggested that home treatment of DVT is now a practical possibility in up to 78 per cent of patients[8], despite an earlier study from the USA in which only 18 per cent of patients were thought to be eligible[9]. The main problems with the concept relate to patient selection and logistics. In some countries, including the UK, community medical and nursing teams may find it difficult to provide treatment that, in the past, has been hospital based. However, an increasing number of hospitals are employing paramedical personnel in the management of DVT. Patients with the suspected diagnosis are first assessed by specialist nurse practitioners rather than doctors.

Protocols such as that described above have made it possible to reduce the number of admissions to hospital and improve patient care. Nurse practitioners do not change jobs as regularly as junior medical staff and so can provide the continuity of care required for the prescribed protocols. Patients at risk of the long-term complications of DVT may be referred to appropriate medical staff.

How might these developments affect surgeons? Vascular surgeons, in particular, see the result of DVT when patients are referred with the postphlebitic syndrome and so should have an interest in their early care at the time of diagnosis of iliofemoral thrombosis. Surgical intervention at this point might improve outcome, thereby reducing future workload. While postphlebitic syndrome may take 20 years to develop, preventing most surgeons from seeing much of the fruit of their labours, it is the patient and not the doctor who is the priority. Vascular surgeons who have access to a vascular laboratory with duplex scanning facilities are well placed to provide a diagnostic service. They and their radiological colleagues already have experience in arterial thrombolysis and so the team should be well equipped for the management of the small number of patients who present with iliofemoral DVT. Surgical thrombectomy might be suitable for those in whom thrombolysis is contraindicated, and improved imaging equipment may aid the selection of patients with postphlebitic syndrome who might benefit from reconstructive deep venous surgery[10]. Undoubtedly, all of these possibilities require further research and this will take many years to accomplish. Nevertheless, funding of such long-term projects is essential in any proper assessment of the place of vascular surgeons in the management of DVT.

References

1 Brandjes DP, Buller HR, Heijboer H, Huisman MV, De Rijk M, Jagt H *et al.* Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; **349:** 759–62.

2 Harris M, Grange J. Management of calf deep venous thrombosis. *Ann Emerg Med* 2000; **35:** 629.

3 Dunn AS, Coller B. Outpatient treatment of deep vein thrombosis: translating clinical trials into practice. *Am J Med* 1999; **106:** 660–9.

4 Anderson DR, Wells PS. Improvements in the diagnostic approach for patients with suspected deep vein thrombosis or pulmonary embolism. *Thromb Haemost* 1999; **82:** 878–86.

5 Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS. Does this patient have deep vein thrombosis? *JAMA* 1998; **279:** 1094–9.

6 Anderson DR, Wells PS, Stiell I, MacLeod B, Simms M, Gray L *et al.* Management of patients with suspected deep vein thrombosis in the emergency department: combining use of a clinical diagnosis model with D-dimer testing. *J Emerg Med* 2000; **19:** 225–30.

7 Buckenham TM. Radiological management of venous thrombosis of the lower limb. *Br J Radiol* 1998; **71:** 353–6.

8 Eikelboom J, Baker R. Routine home treatment of deep vein thrombosis. *BMJ* 2001; **322:** 1192–3.

9 Yusen RD, Haraden BM, Gage BF, Woodward RS, Rubin BG, Botney MD. Criteria for outpatient management of proximal lower extremity deep venous thrombosis. *Chest* 1999; **115:** 972–9.

10 Braithwaite BD. What is new in venous surgery? *Phlebology* 2001; **16:** 3–5.

Review

Molecular mechanisms of renal allograft fibrosis

J. R. Waller and M. L. Nicholson

Division of Transplant Surgery, University of Leicester, Leicester, UK
Correspondence to Dr J. R. Waller, University Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK
(e-mail: julian@waller79.fsnet.co.uk)

Background: Chronic graft nephropathy (CGN) remains the leading cause of renal allograft loss after the first year following transplantation. Histologically it is characterized by glomerulosclerosis, intimal hyperplasia and interstitial fibrosis. The pathogenesis is unclear, but is likely to involve both immunological and non-immunological factors. Despite improvements in short-term graft survival rates, new immunosuppressive regimens have made no impact on CGN.

Methods: A review of the current literature on renal transplantation, novel immunosuppression regimens and advances in the molecular pathogenesis of renal allograft fibrosis was performed.

Results and conclusion: Recent advances in understanding of the underlying molecular mechanisms involved suggest autocrine secretion of cytokines and growth factors, especially transforming growth factor β, are associated with a change in fibroblast phenotype leading to the deposition of extracellular matrix. Repeated insults trigger upregulation of the tissue inhibitors of matrix metalloproteinases, favouring accumulation of extracellular matrix. To date, no drug has proved effective in inhibiting or reducing allograft fibrosis. The deleterious consequences of chronic immunosuppression on the development of such fibrosis are now recognized; newer immunosuppressive drugs, including rapamycin and mycophenolate mofetil, reduce profibrotic gene expression in both experimental and clinical settings, and offer potential strategies for prolonging allograft survival.

Paper accepted 22 June 2001

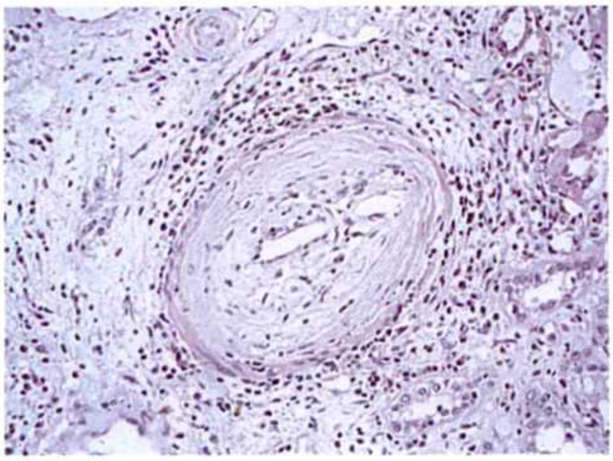
British Journal of Surgery 2001, 88, 1429–1441

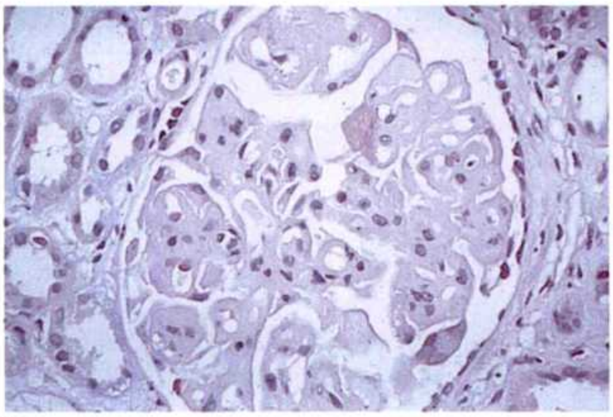
Clinical background

The past two decades have seen considerable improvements in 1-year renal allograft survival rates to over 80 per cent for cadaveric and 90–95 per cent for living related donors[1]. These commendable outcomes may be largely attributed to the introduction of more potent and selective immunosuppressants, such as cyclosporin and tacrolimus, as well as to improvements in understanding of the immunology of transplantation, tissue typing, organ preservation and the management of acute rejection. However, despite reducing the frequency and severity of acute rejection episodes[2], cyclosporin and tacrolimus have had no effect on the development of chronic allograft dysfunction[3], and the half-life of renal allografts has remained unchanged for over a decade[4]. Approximately 50 per cent of transplanted kidneys develop progressive dysfunction within a few months of transplantation, necessitating dialysis or retransplantation within a decade. Data from Leicester show that, despite a 1-year graft survival of about 85 per cent, there is a gradual attrition of 4–5 per cent graft loss per year, leading to 5- and 10-year allograft survival rates of approximately 70 and 50 per cent respectively (M. L. Nicholson, unpublished data). The most common cause of this decline in allograft survival is chronic rejection, perhaps more accurately described as chronic graft nephropathy (CGN). CGN remains the single most important cause of renal allograft failure after the first year following transplantation[5], accounting for some 50–80 per cent of graft losses after this time[6,7]. Recent advances in understanding of the molecular mechanisms of graft fibrosis and the development of novel immunosuppressive agents offer potential new strategies for the prevention and treatment of this important clinical problem.

Clinical presentation and histopathology

Clinically, CGN manifests itself as a progressive deterioration in renal function associated with proteinuria and hypertension in the absence of another specific cause[8]. The deterioration in renal function shows a linear relationship between the reciprocal of serum creatinine concentration and time in more than 80 per cent of patients with histological evidence of CGN[9,10]. A progressive rise in serum creatinine level associated with proteinuria and increased diastolic blood pressure should, therefore, alert the clinician to the possible diagnosis of CGN. However, these are common non-specific findings, with 6–8 per cent of transplant recipients having more than 0·5 g proteinuria per day in the absence of CGN[11]; post-transplant hypertension is also common[12]. The histopathology of CGN is characterized by intimal hyperplasia, glomerulosclerosis, tubular atrophy and interstitial fibrosis[13], associated with a mononuclear cellular infiltrate[14], consisting predominantly of macrophages and T-cell lymphocytes[15] (*Fig. 1*). The dominant underlying pathological process is an excessive accumulation of extracellular matrix proteins leading to fibrosis. Excess extracellular matrix accumulation eventually leads to loss of allograft function and the degree of fibrosis seems to provide the best morphological correlation with renal function and prognosis[16,17].


a Intimal hyperplasia


b Glomerulosclerosis

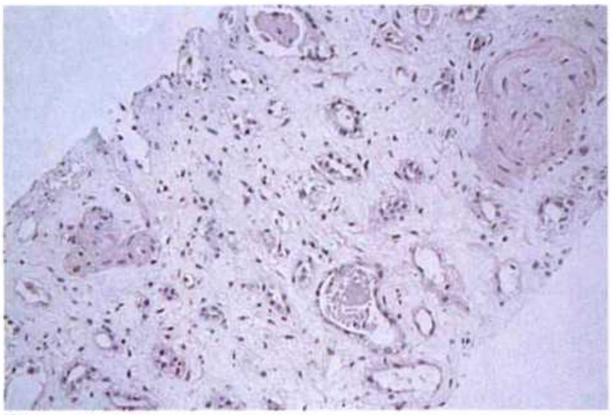

c Interstitial fibrosis

Fig. 1 Histological features of renal allograft fibrosis; **a** Intimal hyperplasia, **b** glomerulosclerosis and **c** interstitial fibrosis (haematoxylin and eosin stain; original magnification **a** × 40, **b** × 40, **c** × 10)

Extracellular matrix

Extracellular matrix proteins can be divided into collagen or non-collagenous classes. The most abundant proteins belong to the collagen family and consist of many different types determined by their α-chain composition. In the kidney, the most important collagen proteins are types I and III, which are fibrillar proteins, and type IV, which is non-fibrillar and the principal component of the basement membrane[18]. The tubulointerstitium contains all three of these collagens, but the glomeruli contain only types III and IV collagen. The interstitial deposition of type I collagen is a late feature of fibrosis and occurs only to a small extent in the kidney. Non-collagenous matrix proteins include the glycoproteins laminin, fibronectin and tenascin, and the proteoglycans, decorin and biglycan. Recent studies have shown an association between the glycoproteins and the overexpression of numerous cytokines. For example, an increased transcription of tenascin and laminin correlates with increased transcription of transforming growth factor (TGF) β in a rat model of diabetes[19].

Extracellular matrix turnover

The extracellular matrix is a dynamic network of proteins and proteoglycans. Under physiological conditions, the synthesis of this matrix is balanced by its degradation (*Fig. 2*). In pathological states an increase in synthesis, a decrease in breakdown, or a combination of both results in an accumulation of matrix, leading to fibrosis. Four families of proteolytic enzymes are involved in the degradation of matrix proteins. The matrix metalloproteinases (MMPs) and serine proteases appear to be the most important, although aspartic and cysteine proteases have an increased role at lower pH.

Matrix metalloproteinases

Over 15 MMPs have now been identified[20]. The most recently discovered are the membrane-type MMPs (MT-MMPs) which are not soluble but contain a transmembrane domain that allows them to attach to cell surfaces[21]. MT-MMPs are not only capable of degrading matrix; they can also activate other metalloproteinases[22]. MMP-2 (gelatinase A, 72 kDa) and MMP-9 (gelatinase B, 92 kDa) have been studied the most in the kidney and are capable of degrading collagen IV, the principal component of the basement membrane.

MMPs are characterized by four features: (1) they are zinc-containing metalloendopeptidases and are inhibited by chelating agents; (2) they are secreted in zymogen form and require extracellular activation; (3) they share common amino acid sequences[23]; and (4) they are inhibited by naturally occurring tissue inhibitors of metalloproteinases (TIMPs). Metalloproteinases 1–15 differ widely in substrate specificity and can be divided into four main subtypes: interstitial collagenases, gelatinases, stromelysins and elastases (*Table 1*). In health, the activity of MMPs is strictly controlled to maintain normal tissue integrity. This control occurs at three levels: transcription, extracellular activation and inhibition.

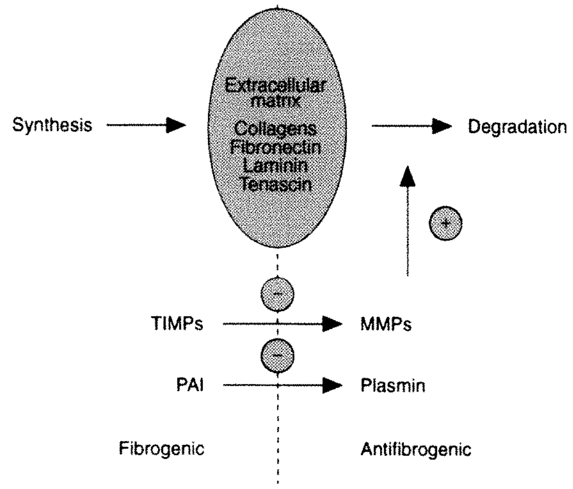


Fig. 2 Turnover of extracellular matrix. MMP, matrix metalloproteinase; PAI, plasminogen activator inhibitor; TIMP, tissue inhibitor of metalloproteinases

Gene expression

With the exception of MMP-9, MMPs are produced constitutively in physiological states, but their expression is also inducible by profibrotic cytokines such as interleukin (IL) 1, and growth factors such as TGF-β and platelet-derived growth factor. IL-1 induces transcription of MMPs through stimulation of a promoter sequence that is shared by the collagenases, stromelysins and gelatinase B[24]. Gelatinase A possesses a different promoter gene sequence which responds to stimulation by TGF-β[25]. Martin *et al.*[26] showed that a combination of IL-1 and TGF-β upregulates all members of the MMP family.

Extracellular activation

With the exception of membrane-bound forms, MMPs are secreted in an inactive form. Activation requires extracellular proteolytic cleavage by plasma proteinases of a propeptide and disruption of a Cys-Zn^{2+} switch[27]. Carmeliet *et al.*[28] demonstrated the importance of the urokinase-type plasminogen activator (uPA)–plasmin system in this process using transgenic mice deficient in uPA. Once activated, members of the MMP family are capable of activating other MMPs[29]. Sato *et al.*[30] demonstrated MT1-MMP to be the major activator of proMMP-2, in addition to its activation by the cell surface-associated uPA–plasmin

Table 1 Matrix metalloproteinases

Subgroup	MMP	Protein	Substrate
Interstitial collagenases	MMP-1	Collagenase 1	Collagens I, III
	MMP-8	Collagenase 2	
	MMP-13	Collagenase 3	
Gelatinases	MMP-2	Gelatinase A	Collagen IV, V Fibronectin
	MMP-9	Gelatinase B	Collagen IV, V
Stromelysins	MMP-3	Stromelysin 1	Collagens I, III Laminin, fibronectin
	MMP-7	Matrilysin	
	MMP-10	Stromelysin 2	
	MMP-11	Stromelysin 3	
Elastinases	MMP-12	Metalloelastase	Elastin
Membrane type	MMP-14	MT1-MMP	ProMMP-2

MMP, matrix metalloproteinase; MT, membrane type system[31]. MMP-2 is unique in this respect, requiring both MT1-MMP and its inhibitor TIMP-1 to form a trimeric compound to become active.

Inhibition

TIMPs are the major endogenous inhibitors of MMP activity. Four homologous TIMPs have been reported to date[32], although most research has concentrated on TIMP-1. TIMPs form a 1 : 1 stoichiometric complex with MMPs, inhibiting both the latent and activated enzyme[33]. TIMP-1, which inhibits all latent MMPs, is not detectable in normal kidneys, but its expression is upregulated in many animal models of renal fibrosis[34–36]. Recent work in the authors' laboratories has demonstrated a direct correlation between TIMP-1 messenger RNA (mRNA), quantified by reverse transcriptase polymerase chain reaction (RT PCR), and collagen III protein expression in protocol renal allograft biopsies (M. L. Nicholson, unpublished data). In contrast, TIMP-2 and TIMP-3 mRNA transcripts are readily detectable in normal kidneys and appear less important in fibrosis. TIMP-2 expression is mainly constitutive[37], while TIMP-3 expression occurs in relation to cell cycle regulation[38]. So far the role of TIMP-4 has not been evaluated in the kidney.

Relaxin is a peptide hormone produced primarily by the corpus luteum in pregnant and non-pregnant females; in pregnancy its production is increased by the placenta and decidua. Its physiological actions include the induction of collagen remodelling with consequent softening of the birth canal and inhibition of uterine contractile activity[39]. Experimental studies have shown that relaxin has a broad spectrum of activity on other tissues and this suggests a potential role in the prevention or reversal of allograft fibrosis. Relaxin induces a matrix degradative phenotype of human lung fibroblasts *in vivo* and inhibits bleomycin-induced pulmonary fibrosis *in vivo* by a dose-dependent upregulation of interstitial collagenase[40]. Fetal membrane explants have been used to assess the effects of exogenous relaxin on metalloproteinase production. MMP-1 gene expression, enzyme and activity were increased by relaxin in a dose-dependent fashion[41]. In addition, a similar response was noted for tissue plasminogen activator, suggesting a coordinated cascade resulting in increased secretion of MMP-1, MMP-3 and MMP-9. However, there was no effect on MMP-2 or TIMP-1 production. Finally, intravenous relaxin reduces myocardial ischaemia–reperfusion injury in rats following ligation of the left anterior descending coronary artery[42]. Interestingly, myocardial neutrophil number and myeloperoxidase activity (a marker of neutrophil accumulation) are both reduced. These findings suggest that relaxin may have organ-protective effects on ischaemia–reperfusion injury, another established risk factor for allograft fibrosis, in addition to its effect on matrix degradation. Experimental studies are warranted to see whether relaxin can reproduce these actions in the kidney.

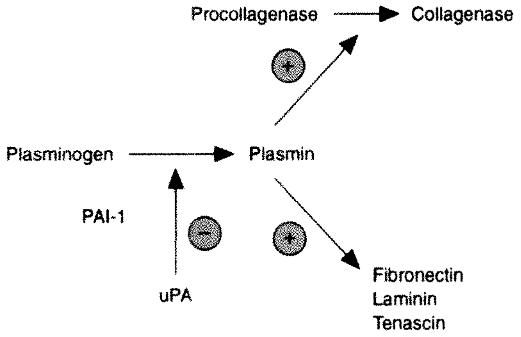


Fig. 3 Plasmin-dependent proteases. PAI, plasminogen activator inhibitor; uPA, urokinase-type plasminogen activator

Urokinase–plasmin

In addition to its role in fibrinolysis, the urokinase–plasmin family also has a major role to play in matrix degradation. Plasminogen undergoes proteolytic cleavage to become active plasmin, which activates procollagenases and is capable of degrading laminin, fibronectin and tenascin (*Fig. 3*). Although most plasminogen is synthesized in the liver, plasminogen mRNA expression has been localized to the kidney[43]. Plasminogen is activated by uPA, which is synthesized by proximal and distal tubular epithelial cells. Its activity is opposed by its naturally occurring inhibitor, plasminogen activator inhibitor (PAI) 1, which is upregulated in animal models of fibrosis[44–46], although its direct effect on fibrosis in renal allografts remains to be proven.

Renal allograft response to injury

The kidney sustains numerous insults during transplantation that result in decreased allograft mass and fibrotic changes. These include brain-death injury[47], warm and cold ischaemia[48], ischaemia–reperfusion injury[49], acute rejection episodes[50], prolonged exposure to nephrotoxic drugs[51], recipient lipid abnormalities[52], hypertension[53], diabetes mellitus[54] and cytomegalovirus infection[55]. The kidney responds to this injury phase by initiating repair mechanisms that lead to an influx of mononuclear cells, proliferation of fibroblasts and deposition of extracellular matrix, leading to scar formation or fibrosis. Macrophage infiltrates are commonly present in fibrotic allografts and are key mediators in initiating fibrosis by providing a wealth of profibrotic factors and extracellular matrix proteins[56]. Fibroblasts are also thought to be particularly important in fibrogenesis[57] and fibroblasts cultured from diseased kidneys have been shown to deposit more collagen than normal fibroblasts[58]. During fibrogenesis numerous cytokines and growth factors stimulate fibroblasts to become myofibroblasts[59]. This latter cell type, characterized by expression of smooth muscle cell proteins such as smooth muscle cell α-actin[60], becomes the main cellular component of the interstitium[61]. This phenotypic switch from a quiescent to a secretory state is a pivotal cellular event in the accumulation of extracellular matrix.

The origin of interstitial fibroblasts remains unclear as they demonstrate poor antigenicity and a paucity of cell markers. None the less, electron microscopic studies have suggested that fibroblast or fibroblast-like cells originate from resident cells in the interstitium[62]. More recently, differential and subtractive hybridization of transcripts from renal tubular epithelium has characterized fibroblast-specific protein (FSP) 1[63], which has a role in the motility of fibroblasts through its interaction with cytoskeletal actin and tubulin[64]. This new marker has been used to demonstrate a paucity of macrophage activity in the interstitium under physiological conditions. In contrast, in a mouse model of interstitial fibrosis there was a significant increase in uptake of FSP-1, which correlated with increased collagen deposition detected by trichrome staining[65]. Moreover, a reduction in profibrotic stimuli induces myofibroblasts to return to their former quiescent state or undergo apoptosis[66].

The role of tubular epithelial cells in the production of extracellular matrix in allograft fibrosis is unclear. Physiologically these cells are responsible for the matrix production of the basement membrane, but experimental models have shown that tubuloepithelial cells produce matrix in response to profibrotic stimuli. Upregulation of tubular collagen IV has been demonstrated in diabetic rats[67] and TGF-β-stimulated rabbit proximal tubular cells increase synthesis of proteoglycan and fibronectin[68]. Tubular epithelial cells also undergo phenotypic changes in response to profibrotic cytokines and growth factors. Their ability to transdifferentiate *in vivo* has been shown by Strutz *et al.*[69], who demonstrated *de novo* expression of FSP-1, suggesting differentiation into fibroblasts.

Profibrotic signals

Numerous profibrotic cytokines, adhesion molecules and growth hormones are released into the circulation in response to injuries sustained during or after renal transplantation (*Table 2*). Their net effect tilts the balance of synthesis and degradation of extracellular matrix in favour of accumulation, leading to fibrosis and subsequent graft failure. Of these, TGF-β and angiotensin II appear to be the most potent profibrotic mediators; they have been the most extensively studied.

Transforming growth factor β

TGF-β is a potent profibrotic cytokine signalling molecule that is essential for normal wound healing[85]. It is released as a latent precursor after tissue injury. The molecule is non-covalently bound to latency-associated peptide[86], which must be cleaved before TGF-β can bind to its receptors[87]. A

Table 2 Profibrotic signals in allograft fibrosis

Cytokine	Major functions
Interleukin 1	Upregulation of adhesion molecules on endothelial cells[70]
	Induces smooth muscle cell and fibroblast proliferation and PDGF-A gene expression[71,72]
Interleukin 6	Mitogen for smooth muscle and mesangial cells (implicated in development of allograft intimal hyperplasia)[73]
TNF-α	Stimulates leucocyte and endothelial cell production of adhesion molecules and other cytokines[74]
	Increases ECM by downregulation of ECM proteases and upregulation of TIMPs
Adhesion molecules	Upregulation of ICAM-1 and VCAM-1 on tubular cells and glomerular endothelium (mediate mononuclear cell infiltration)[75,76]
PDGF	Potent smooth muscle cell chemoattractant and mitogen[77]
	Macrophage chemoattractant and induces phenotypic change of fibroblasts to myofibroblasts[78]
bFGF	Chemoattractant and mitogen for vascular smooth muscle cells[79]
	Increased expression of bFGF in human renal biopsies and animal models of renal fibrosis[80–82]
TGF-β	Stimulation of ECM protein deposition, upregulation of protease inhibitors and integrin expression[83]
Angiotensin II	Increases ECM deposition via TGF-β
	Induces upregulation of PAI-1
Endothelin 1	Stimulates proliferation of human renal fibroblasts[84]

PDGF, platelet-derived growth factor; TNF, tumour necrosis factor; ECM, extracellular matrix; TIMP, tissue inhibitor of metalloproteinases; ICAM, interstitial cellular adhesion molecule; VCAM, vascular cellular adhesion molecule; bFGF, basic fibroblast growth factor; TGF, transforming growth factor; PAI, plasminogen activator inhibitor

deficiency of TGF-β is inconsistent with life and Kulkarni *et al.*[88] showed that transgenic mice deficient in TGF-β died from systemic autoimmune-like illnesses once circulating maternal TGF-β had disappeared. The molecule is normally released transiently in response to a single isolated injury and so its actions are limited, resulting in tissue healing as opposed to fibrosis[83].

Conversely, sustained or increased synthesis of TGF-β results in a shift towards accumulation of extracellular matrix by increasing matrix synthesis and inhibiting its degradation. TGF-β-stimulated fibroblasts increase synthesis of most matrix proteins, including collagen, fibronectin and proteoglycans[89]. In addition, TGF-β decreases expression of matrix proteolytic enzymes and upregulates their specific inhibitors, thus furthering matrix accumulation[90,91]. Finally, TGF-β exhibits positive autoregulation of its own synthesis, thereby augmenting its fibrogenic actions[92]. Several properties of TGF-β suggest that it may have a prominent role in allograft fibrosis: (1) stimulation of the production of extracellular matrix proteins; (2) promotion of the production of protease inhibitors, such as PAI-1; (3) upregulation of integrin expression; and (4) reduction in the activity of matrix-degrading proteins[93].

Ex vivo and *in vivo* models have been used to demonstrate the fibrogenic consequences of prolonged TGF-β stimulation[94–96]. Intravenous administration of recombinant TGF-β produces rapid glomerulosclerosis in rats and rabbits[97]. Increased renal allograft expression of TGF-β also occurs in the clinical setting[98,99]. Nicholson *et al.*[100] examined intragraft gene expression in glomeruli using a RT PCR and found a positive correlation between the level of glomerular complementary DNA for TGF-β and renal cortical collagen III immunostaining ($P < 0{\cdot}01$). Intragraft TGF-β levels also correlate with a decline in allograft function. Cuhaci *et al.*[101] identified two populations of patients determined by their level of TGF-β expression. Those with low levels of TGF-β demonstrated a mean decline in renal function of 6·2 ml per min per year while those with high levels had a mean decline of 19·5 ml per min per year ($P < 0{\cdot}05$), suggesting a threefold acceleration in loss of renal function.

Recently, genetic polymorphisms for the leader sequence of the TGF-β_1 protein have been identified in lung transplant recipients[102,103]. These are located at codon 10 (leucine or proline) and codon 25 (arginine or proline). An increased prevalence of homozygosity for arginine at codon 25 occurred in pretransplant patients and was associated with a poor post-transplant survival. A similar relationship has not yet been explored in renal allografts.

Angiotensin II

Beyond its role in the regulation of glomerular haemodynamics, the intrarenal renin–angiotensin system has been recognized as a growth promotor that contributes to growth and sclerosis in various organs[104–106]. Cellular responses to angiotensin II are mediated by specific membrane receptors, of which four have been cloned. Angiotensin type 1 (AT_1) receptors are expressed on vascular smooth muscle cells ubiquitously, and are responsible for the central and peripheral effects of angiotensin II on blood pressure, osmoregulation and cell growth[107]. The main effect on the glomerulus is pronounced vasoconstriction, affecting the efferent arteriole to a greater extent than the afferent, thereby maintaining the glomerular filtration rate in the presence of renal hypoperfusion. AT_2 receptors are present in high concentrations only in the adult human adrenal medulla, uterus, ovary, vascular endothelium and specific brain areas[108]. The AT_2 receptor is thought to be involved in inhibiting cell proliferation and apoptosis[109].

Several animal models have provided evidence of the profibrotic actions of angiotensin II. Chronic angiotensin infusion in rats results in interstitial fibrosis[110] and the addition of angiotensin II to cultured vascular smooth muscle cells leads to an increased secretion of TGF-β[111]. Angiotensin II-stimulated rat glomerular mesangial cells increase extracellular matrix deposition and this is also mediated by an increase in TGF-β[112]. Studies showing the development of glomerulosclerosis in the absence of glomerular hypertension, and the attenuation of sclerosis by angiotensin-converting enzyme inhibitors without lowering intraglomerular pressure, suggest that the profibrotic effects of angiotensin II are independent of its hypertensive effects[113,114]. These effects are not reproduced by other antihypertensives and appear to be related specifically to the antagonism of angiotensin II[115].

Intraglomerular hypertension can lead to early allograft failure. Glomerular hypertension may result from an increase in systemic pressure in association with a reduced renal mass, occurring as a result of acute rejection episodes and chronic cyclosporin nephrotoxicity[116]. Evidence is emerging that the renin–angiotensin system may mediate chronic cyclosporin nephrotoxicity. Using a rat salt-depleted model of chronic cyclosporin nephrotoxicity, Shihab *et al.*[117] showed that cyclosporin-induced interstitial fibrosis could be reversed by losartan and enalapril. The effects of angiotensin II receptor blockade in renal transplant recipients have been studied in two clinical trials. Calvino *et al.*[118] studied the antiproteinuric effect of losartan on 18 stable renal transplant patients with hypertension for a mean follow-up of 76 months. In addition to its antihypertensive properties (a reduction in mean arterial pressure of 10 mmHg; $P < 0.001$), mean proteinuria was significantly reduced by losartan from 1·0 to 0·4 g/l ($P < 0.003$). In the other trial 14 patients with histological evidence of CGN were treated with losartan and followed for 8 weeks[119]. Again there was a significant decrease in mean arterial blood pressure (of 15 mmHg; $P < 0.05$) and a significant decrease in clinically relevant proteinuria in five patients (from a mean of 3·5 to1·9 g per 24 h; $P < 0.05$); these effects were accompanied by a mean 54·6 per cent reduction below baseline level of serum TGF-β ($P < 0.05$). To date, however, there have been no large clinical trials of angiotensin-converting enzyme inhibitors or receptor antagonists relating to renal transplant fibrosis and long-term renal function.

Finally, angiotensin has been shown to induce PAI-1[120,121]. This is mediated by angiotensin IV, the angiotensin hexapeptide metabolite of angiotensin II, and occurs via the AT_1 receptor[122]. Both plasmin and uPA are proteolytic, either directly or via their activation of latent metalloproteinases[123], and so their inhibition by PAI-1 results in the accumulation of extracellular matrix proteins.

Immunosuppressive drugs

It is now recognized that immunosuppressive drugs may contribute to the development of allograft fibrosis[124]. Although cyclosporin and steroids are standard therapy for transplanted patients, both are known to cause an upregulation of TGF-β[125,126]. Long-term administration of the calcineurin inhibitors cyclosporin and tacrolimus is known to produce histological changes similar to those of allograft fibrosis[127,128]. In addition, these drugs induce hyperlipidaemia[129], hypertension[130] and diabetes[131], all established risk factors for CGN. In a randomized open-label trial comparing tacrolimus with cyclosporin, there was a significant reduction in the incidence and severity of biopsy-proven acute rejection episodes in the tacrolimus group[132]. While the 1-year graft survival rates were similar, the long-term benefit of reduced acute rejection episodes remains to be reported in this group. Recent work in the authors' department has, however, shown a reduction in profibrotic gene expression associated with tacrolimus administration[133,134]. In a rodent model of ischaemia–reperfusion injury, Jain *et al.*[133] showed significantly less proteinuria and lower serum creatinine levels in animals receiving tacrolimus than in those receiving cyclosporin ($P < 0.05$). Both TGF-β and TIMP-1 expression were significantly reduced in the tacrolimus group compared with controls ($P < 0.05$ and $P < 0.007$ respectively); this was not the case with cyclosporin ($P < 0.07$ for both variables). Differential effects on profibrotic gene expression in isolated glomeruli from protocol biopsies have since been demonstrated in a prospective randomized trial comparing cyclosporin and tacrolimus[134]. The levels of collagen III and TIMP-1 expression were significantly lower in the tacrolimus group than in the cyclosporin-treated group ($P < 0.01$). There were, however, no significant differences in mRNA expression for collagen IV, TIMP-2, MMP-2 or TGF-β. As TIMP-1 expression in the tacrolimus group was not associated with any significant change in MMP expression, the balance of extracellular matrix turnover showed a shift in favour of matrix degradation in comparison to cyclosporin. In addition, there was a reduction in collagen III expression in the tacrolimus group. Collagen III deposition in biopsies taken at 6 months is currently under assessment, with a view to correlating the results with final graft survival times[135].

Newer immunosuppressive drugs have been introduced in an attempt to prolong graft survival. Mycophenolate mofetil is a potent non-competitive inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the *de novo* synthesis of guanosine[136]. It inhibits lymphocyte proliferation and downregulates adhesion molecules, macrophages, lymphocytes and proliferation of vascular smooth muscle cells[137–139]. In one clinical study of its use in conjunction with cyclosporin, despite a reduction in the incidence of acute rejection by 50 per cent compared with azathioprine or placebo[140,141], there was no statistically significant difference in renal function or proteinuria at 3 years[142]. Thus mycophenolate mofetil may not have an impact in the prevention of CGN when used in conjunction with calcineurin inhibitors. However, smaller trials have suggested that its addition in patients with CGN may slow the decline in renal function[143–145]. Islam *et al.*[146] followed 43 patients who were at least 6 months after transplantation and who had more than a 20 per cent increase in serum creatinine level above baseline value. Patients were commenced on mycophenolate mofetil 1 g twice daily and the cyclosporin dosage was gradually reduced over 2 weeks to a target trough level of 50 ng/ml. Those taking azathioprine were changed to mycophenolate mofetil before reducing cyclosporin. After addition of the new drug for a mean of 15 (range 6–22) months, mean serum creatinine level improved significantly from 3·14 to 2·57 mg/dl ($P < 0.01$). Five patients were withdrawn from the study because of side-effects (three with diarrhoea, one with anaemia and one with gastroduodenal ulcers) and two progressed to end-stage renal failure. Therefore, mycophenolate mofetil may be introduced to allow a reduction of calcineurin inhibitors and lessen their nephrotoxic effects.

More recently, much interest has developed in rapamycin, a macrolide antibiotic derived from *Streptomyces hygroscopicus*. *In vitro* studies have shown that it inhibits growth factor-stimulated cell progression from the G1 phase of the cell cycle and DNA synthesis[147,148]. The antiproliferative effect of rapamycin on stimulated vascular smooth muscle cells is superior to that of cyclosporin, tacrolimus and mycophenolate mofetil[149,150]. Morris *et al.*[151] showed that rapamycin effectively reduces arterial thickening in a 'mechanical' balloon angioplasty model of intimal hyperplasia. These effects were reproduced in an 'inflammatory' model of CGN using femoral allografts in the same study. Animal and *in vitro* studies have demonstrated that rapamycin and cyclosporin act synergistically to prolong allograft survival[152]. This synergism was investigated in a multicentre trial in the USA that compared rapamycin with azathioprine in conjunction with prednisolone and cyclosporin[153]. Six-month rejection rates were significantly lower in the rapamycin groups at 17 per cent for those receiving 2 mg of the drug per day and 12 per cent for those receiving 5 mg/day, compared with 30 per cent for those taking azathioprine 2·5 mg per kg per day. However, serum creatinine levels were unexpectedly higher at 6 months in the rapamycin groups (154·2 µmol/l at 2 mg/day and 157·6 µmol/l at 5 mg/day) than in the azathioprine group (129·4 µmol/l). These statistically highly significant differences were attributed to rapamycin increasing cyclosporin levels with a consequent increase in nephrotoxicity. So, if rapamycin is to be used in conjunction with a calcineurin inhibitor, the dose of the calcineurin inhibitor should be reduced accordingly and careful attention paid to whole blood drug levels. Despite its efficacy in inhibiting acute rejection and proliferation[138,154,155], rapamycin's role in the prevention of allograft fibrosis may be counteracted by its hypercholesterolaemic and hyperlipidaemic effects[143]. Clinical trials on rapamycin are under way, although so far none is assessing the impact of rapamycin on CGN.

Conclusion

CGN remains the leading cause of graft failure after the first year following transplantation. At present no effective drug is available to inhibit or reverse this process. However, a better understanding of the molecular mechanisms involved offers a number of potential new strategies. Partial inhibition of TIMP-1 and TGF-β may prove effective in reducing fibrosis and prolonging allograft survival. Larger randomized studies are required to assess whether or not angiotensin-converting enzyme inhibitor and angiotensin II receptor antagonist therapies have beneficial effects after kidney transplantation. Relaxin offers some potential as a biological solution to excessive extracellular matrix deposition. Finally, newer immunosuppressive agents, such as mycophenolate mofetil and rapamycin, may allow the design of immunosuppressive regimens in which calcineurin inhibitors can be withdrawn early after transplantation or even avoided altogether.

Acknowledgements

The photomicrographs (*Fig. 1*) were kindly provided by Dr P. N. Furness. Dr J. R. Waller is a Buckston Browne Surgical Research Fellow for the Royal College of Surgeons of England.

References

1 Paul LC. Chronic allograft nephropathy – a model of impaired repair from injury? *Nephrol Dial Transplant* 2000; **15:** 149–51.
2 Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998; **338:** 161–5.
3 Bicknell GR, Williams ST, Shaw JA, Pringle JH, Furness PN, Nicholson ML. Differential effects of cyclosporin and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants. *Br J Surg* 2000; **87:** 1569–75.
4 Campistol JM, Sacks SH. Mechanisms of nephrotoxicity. *Transplantation* 2000; **69**(Suppl 12): SS5–10.
5 Dennis MJS, Foster MC, Ryan JJ, Burden RP, Morgan AG, Blamey RW. The increasing importance of chronic rejection as a cause of renal allograft failure. *Transpl Int* 1989; **2:** 214–17.
6 Bergmann L, Roper L, Bow LM, Hull D, Bartus SA, Schweizer RT. Late graft loss in cadaveric renal transplantation. *Transplant Proc* 1992; **24:** 2718–19.
7 Matas AJ, Gillingham KJ, Sutherland DER. Half-life and risk factors for kidney transplant outcome – importance of death with function. *Transplantation* 1993; **55:** 757–61.
8 Paul LC, Hayry P, Foegh M, Dennis MJ, Mihatsch MJ, Larsson E *et al.* Diagnostic criteria for chronic rejection/accelerated graft atherosclerosis in heart and kidney transplants: joint proposal from the Fourth Alexis Carrel Conference on Chronic Rejection and Accelerated Arteriosclerosis in Transplanted Organs. *Transplant Proc* 1993; **25:** 2022–3.
9 Modena FM, Hostetter TH, Salakudeen AK, Najarian JS, Matas AJ, Rosenberg ME. Progression of kidney disease in chronic renal transplant rejection. *Transplantation* 1991; **52:** 239–44.
10 Kasiske BL, Heim-Duthoy KL, Tortorice KL, Rao KV. The variable nature of chronic declines in renal allograft function. *Transplantation* 1991; **51:** 330–4.
11 Massy ZA, Guijarro C, Weiderkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int* 1996; **49:** 518–24.

12 Raine AEG. Does antihypertensive therapy modify chronic allograft failure? *Kidney Int* 1995; **48**(Suppl 52): S107–11.

13 Kasiske BL, Kabil RSN, Lee HS, Rao KV. Histopathological findings associated with a chronic, progressive decline in renal allograft function. *Kidney Int* 1991; **80**: 514–24.

14 Sanfilippo F. Renal transplantation. In: Sale GE, ed. *The Pathology of Organ Transplantation*. Boston, Massachusetts: Butterworths, 1990: 51–101.

15 Mason DW, Morris PJ. Effector mechanisms in allograft rejection. *Annu Rev Immunol* 1986; **4**: 119–45.

16 Risdon RA, Sloper JC, De Wardener HE. Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet* 1968; **ii**: 363–6.

17 Fine LG, Norman JT, Ong A. Cell–cell cross talk in the pathogenesis of renal interstitial fibrosis. *Kid Int Suppl* 1995; **49**: S48–50.

18 Furness PN. Extracellular matrix and the kidney. *J Clin Pathol* 1996; **49**: 355–9.

19 Yang CW, Hatton M, Vlassara H, He CJ, Carome MA, Yamoto E *et al.* Overexpression of transforming growth factor-beta 1 mRNA is associated with up-regulation of glomerular tenascin and laminin in nonobese diabetic mice. *J Am Soc Nephrol* 1995; **5**: 1610–17.

20 Nagase H, Woessner JF. Matrix metalloproteinases. *J Biol Chem* 1999; **274**: 21 491–4.

21 Ye S, Humphries S, Henney A. Matrix metalloproteinases: implication in vascular matrix remodelling during atherogenesis. *Clin Sci* 1998; **94**: 103–10.

22 Sato H, Takino T, Okado Y, Cao J, Shinagawa A, Yamamoto E *et al.* A matrix metalloproteinase expressed on the surface of invasive tumour cells. *Nature* 1994; **370**: 61–5.

23 Matrisian LM. Metalloproteinases and their inhibitors in matrix remodeling. *Trends Genet* 1990; **6**: 121–5.

24 Katsura M, Ito A, Hirakawa S, Mori Y. Human recombinant interleukin-1α increases biosynthesis of collagenase and hyaluronic acid in cultured human chorionic cells. *FEBS Lett* 1989; **244**: 315–18.

25 Salo T, Turpeeniemi-Hujanen R, Tryggvason K. Tumor-promoting esters and cell proliferation stimulate secretion of basement membrane (type IV) collagen-degrading metalloproteinase by human fibroblasts. *J Biol Chem* 1985; **260**: 8526–31.

26 Martin J, Knowlden J, Davies M, Williams JD. Identification and dependent regulation of human mesangial cell metalloproteinases. *Kidney Int* 1994; **46**: 877–85.

27 Nagase H. Activation mechanisms of matrix metalloproteinases. *Biol Chem* 1997; **378**: 151–60.

28 Carmeliet P, Moons L, Lijnen R, Baes M, Lemaitre V, Tipping P *et al.* Urokinase-generated plasmin activates matrix metalloproteinases during aneurysm formation. *Nat Genet* 1997; **17**: 439–44.

29 Crabbe T, Smith B, O'Connell JP, Docherty A. Human progelatinase A can be activated by matrilysin. *FEBS Lett* 1994; **345**: 14–16.

30 Sato H, Takino T, Okada Y, Cao J, Shinagawa A, Yamamoto E *et al.* A matrix metalloproteinase expressed on the surface of invasive tumour cells. *Nature* 1994; **370**: 61–5.

31 Mazzieri R, Masiero L, Zanetta L, Monea S, Onisto M, Garbisa S *et al.* Control of type IV collagenase activity by components of the urokinase–plasmin system: a regulatory mechanism with cell-bound reactants. *EMBO J* 1997; **16**: 2319–32.

32 Gomez DE, Alonso DF, Yoshiji H, Thorgeirsson UP. Tissue inhibitors of metalloproteinases: structure, regulation and biological functions. *Eur J Cell Biol* 1997; **74**: 111–22.

33 Murphy G, Willenbrock F. Tissue inhibitors of matrix metalloendopeptidases. *Methods Enzymol* 1995; **248**: 496–510.

34 Tang WW, Feng L, Xia Y, Wilson CB. Extracellular matrix accumulation in immune-mediated tubulointerstitial injury. *Kidney Int* 1994; **45**: 1077–84.

35 Duymelinck C, Deng JT, Dauwe SE, De Broe ME, Verpooten GA. Inhibition of the matrix metalloproteinase system in a rat model of cyclosporine nephropathy. *Kidney Int* 1998; **54**: 804–18.

36 Sharma AK, Mauer SM, Kim Y, Michael AF. Altered expression of matrix metalloproteinase-2, TIMP, and TIMP-2 in obstructive nephropathy. *J Lab Clin Med* 1995; **125**: 754–61.

37 Stetler-Stevenson WG, Brown PD, Onisto M, Levy AT, Liotta LA. Tissue inhibitor of metalloproteinases-2 (TIMP-2) mRNA expression in tumor cell lines and human tumor tissues *J Biol Chem* 1990; **265**: 13 933–8.

38 Wick M, Burger C, Brusselbach S, Lucibello FC, Muller R. A novel member of human tissue inhibitor of metalloproteinases (TIMP) gene family is regulated by G_1 progression, mitogenic stimulation, differentiation, and senescence. *J Biol Chem* 1994; **269**: 18 953–60.

39 Bani D. Relaxin: a pleiotropic hormone. *Gen Pharmacol* 1997; **28**: 13–22.

40 Unemori EN, Pickford LB, Salles AL, Piercy CE, Grove BH, Erikson ME *et al.* Relaxin induces an extracellular matrix-degrading phenotype in human lung fibroblasts *in vitro* and inhibits lung fibrosis in a murine model *in vivo*. *J Clin Invest* 1996; **98**: 2739–45.

41 Qin X, Garibay Tupas J, Chua PK, Cachola L, Bryant-Greenwood GD. An autocrine/paracrine role of human decidual relaxin. I. Interstitial collagenase (matrix metalloproteinase-1) and tissue plasminogen activator. *Biol Reprod* 1997; **56**: 800–11.

42 Bani D, Masini E, Bello MG, Bigazzi M, Sacchi TB. Relaxin protects against myocardial injury caused by ischemia and reperfusion in rat heart. *Am J Pathol* 1998; **152**: 1367–76.

43 Meroni G, Buraggi G, Mantovani R, Taramelli R. Motifs resembling hepatocyte nuclear factor 1 and activator protein 3 mediate the tissue specificity of human plasminogen gene. *Eur J Biochem* 1996; **236**: 373–82.

44 Eddy AA, Giachelli CM. Renal expression of genes that promote interstitial inflammation and fibrosis in rats with protein-overload proteinuria. *Kidney Int* 1995; **47**: 1546–57.

45 Shihab FS, Bennett WM, Tanner AM, Andoh TF. Mechanism of fibrosis in experimental tacrolimus nephrotoxicity. *Transplantation* 1997; **64:** 1829–37.

46 Shihab FS, Tanner AM, Shao Y, Weffer MI. Expression of TGF-β1 and matrix proteins is elevated in rats with chronic rejection. *Kidney Int* 1996; **50:** 1904–13.

47 Takada M, Nadeau KC, Hancock WW, Mackenzie HS, Shaw GD, Waaga AM *et al.* Effects of explosive brain death on cytokine activation of peripheral organs in the rat. *Transplantation* 1998; **65:** 1533–42.

48 Troppmann C, Gillingham KJ, Benedetti E, Almond PS, Gruessner JS, Najarian JS *et al.* Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. The multivariate analysis. *Transplantation* 1995; **59:** 962–8.

49 Shoskes D, Cecka JM. Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 1998; **66:** 1697–701.

50 Matas A. Chronic rejection in renal transplant recipients – risk factors and correlates. *Clin Transplant* 1994; **8:** 332–5.

51 Gjertson DW. Survival trends long-term first cadaver-donor kidney transplants. In: Terasaki P, Cecka JM, eds. *Clinical Transplants 1001.* Los Angeles, California: UCLA Tissue Typing Laboratory, 1992: 225–35.

52 Isoniemi H, Nurminen M, Tikkanen MJ, von Willebrand E, Krogerus L, Ahonen J *et al.* Risk factors predicting chronic rejection of renal allografts. *Transplantation* 1994; **57:** 68–72.

53 Cheigh JS, Haschemeyer RH, Wang JC, Riggio RR, Tapia L, Stenzel KH *et al.* Hypertension in kidney transplant recipients. Effect of long-term renal allograft survival. *Am J Hypertens* 1989; **2:** 341–8.

54 Lim EC, Terasaki PI. Outcome of renal transplantation in different primary diseases. In: Terasaki P, ed. *Clinical Transplants 1991.* Los Angeles, California: UCLA Tissue Typing Laboratory, 1991: 153–257.

55 Reinke P, Fietze E, Ode-Hakim S, Prosch S, Lippert J, Ewert R *et al.* Late-acute renal allograft rejection and symptomless cytomegalovirus infection. *Lancet* 1994; **344:** 1737–8.

56 Nathan CF. Secretory products of macrophages. *J Clin Invest* 1987; **79:** 319–26.

57 Desmouliere A, Gabbiani G. Myofibroblast differentiation during fibrosis. *Exp Nephrol* 1995; **3:** 134–9.

58 Stetler-Stevenson WG. Dynamics of matrix turnover during pathologic remodeling of the extracellular matrix. *Am J Pathol* 1996; **148:** 1345–50.

59 Grinnell F. Fibroblasts, myofibroblasts, and wound contraction. *J Cell Biol* 1994; **124:** 401–4.

60 Darby I, Skalli O, Gabbiani G. α-Smooth muscle cell actin is transiently expressed by myofibroblasts during experimental wound healing. *Lab Invest* 1990; **63:** 21–9.

61 Border WA, Noble NA. Transforming growth factor-β in tissue fibrosis. *N Engl J Med* 1994; **331:** 1286–92.

62 Ross R. The connective tissue fiber forming cell. In: Gould BS, ed. *Treatise on Collagen.* Vol. 2. Part A. London: Academic Press, 1968: 1–82.

63 Strutz F, Okada H, Lo CW, Danoff T, Carone B, Tomazewski JE *et al.* Identification and characterization of a fibroblast marker FSP1. *J Cell Biol* 1995; **130:** 393–405.

64 Takenaga K, Nakamura Y, Endo H, Sakiyama S. Involvement of S100-related calcium-binding protein pEL98 (or mts1) in cell motility and tumor cell invasion. *Jpn J Cancer Res* 1994; **85:** 831–9.

65 Haverty TP, Kelly CJ, Hines WH, Amenta PS, Watanabe M, Harper RA *et al.* Characterization of a renal tubular cell line which secretes the autologous target antigen of autoimmune experimental interstitial nephritis. *J Cell Biol* 1988; **107:** 1359–68.

66 Clark RAF. Regulation of fibroplasia in cutaneous wound repair. *Am J Med Sci* 1993; **306:** 42–8.

67 Ceol M, Nerlich A, Baggio B, Anglani F, Sauer U, Schleicher E *et al.* Increased glomerular α1 (IV) collagen expression and deposition in long-term diabetic rats is prevented by chronic glycosaminoglycan treatment. *Lab Invest* 1996; **74:** 484–95.

68 Humes HD, Nakamura T, Cieslinski DA, Miller D, Emmons RV, Border WA. Role of proteoglycans and cytoskeleton in the effects of TGF-beta 1 on renal proximal tubule cells. *Kidney Int* 1993; **43:** 575–84.

69 Strutz F, Muller GA, Neilson EG. Transdifferentiation: a new angle on renal fibrosis. *Exp Nephrol* 1996; **4:** 267–70.

70 di Giovine FS, Duff GW. Interleukin 1: the first interleukin. *Immunol Today* 1990; **11:** 13–20.

71 Raines EW, Dower SK, Ross R. Interleukin-1 mitogenic activity for fibroblasts and smooth muscle cells is due to PDGF-AA. *Science* 1989; **243:** 393–6.

72 Nikolic-Paterson DJ, Main IW, Tesch GH, Lan HY, Atkins RC. Interleukin-1 in renal fibrosis. *Kidney Int Suppl* 1996; **54:** S88–90.

73 Ruef C, Budde K, Lacy J, Northemann W, Baumann M, Sterzel RB *et al.* Interleukin 6 is an autocrine growth factor for mesangial cells. *Kidney Int* 1990; **38:** 249–57.

74 Paulnock DM. Macrophage activation by T cells. *Curr Opin Immunol* 1992; **4:** 344–9.

75 Gibbs P, Berkley LM, Bolton EM, Briggs JD, Bradley JA. Adhesion molecule expression (ICAM-1, VCAM-1, E-selectin and PCAM) in human kidney allografts. *Transpl Immunol* 1993; **1:** 109–13.

76 Hancock WH, Whitley WD, Tullius SG, Heeman UW, Wasowska B, Baldwin WM III *et al.* Cytokines, adhesion molecules, and the pathogenesis of chronic rejection of rat renal allografts. *Transplantation* 1993; **56:** 643–50.

77 Thyberg J, Hedin U, Sjolund M, Palmberg L, Bottger BA. Regulation of differentiated properties and proliferation of arterial smooth muscle cells. *Arteriosclerosis* 1990; **10:** 966–90.

78 Tang WW, Ulich TR, Lacey DLK, Hill DC, Qi M, Kaufman SA *et al.* Platelet-derived growth factor-BB induces renal tubulointerstitial myofibroblast formation and tubulo-interstitial fibrosis. *Am J Pathol* 1996; **148:** 1169–80.

79 Lindner V, Lappi DA, Baird A, Majack RA, Reidy MA. Role of basic fibroblast growth factor in vascular lesion formation. *Circ Res* 1991; **68:** 106–13.

80 Ray PE, Bruggeman LA, Weeks BS, Kopp JB, Bryant JL, Owens JW *et al.* bFGF and its low affinity receptors in the

pathogenesis of HIV-associated nephropathy in transgenic mice. *Kidney Int* 1994; **46**: 759–72.

81 Morita H, Shinzato T, David G, Mizutani A, Habuchi H, Fujita Y *et al.* Basic fibroblast growth factor-binding domain of heparin sulphate in the human glomerulosclerosis and renal tubulointerstitial fibrosis. *Lab Invest* 1994; **71**: 528–35.

82 Ichimura T, Maier JA-M, Maciag T, Zhang G, Stevens JL. FGF-1 in normal and regenerating kidney: expression in mononuclear, interstitial, and regenerating epithelial cells. *Am J Physiol* 1995; **269**: F653–62.

83 Border WA, Ruoslahti E. Transforming growth factor-β in disease: the dark side of tissue repair. *J Clin Invest* 1992; **90**: 1–7.

84 Ong ACM, Jowett TP, Firth JD, Burton S, Kitamura M, Fine LG. Human tubular-derived endothelin in the paracrine regulation of renal interstitial fibroblast function. *Exp Nephrol* 1994; **2**: 134 (Abstract).

85 Sporn MB, Roberts AB. Transforming growth factor β: recent progress and new challenges. *J Cell Biol* 1992; **119**: 1017–21.

86 Waltenberger J, Miyazono K, Funa K, Wanders A, Fellstrom B, Heldin CH. Transforming growth factor-beta and organ transplantation. *Transplant Proc* 1993; **25**: 2038–40.

87 Munger JS, Harpel JG, Gleizes PE, Mazzieri R, Nunes I, Rifkin DB. Latent transforming growth factor-β: structural features and mechanisms of activation. *Kidney Int* 1997; **51**: 1376–82.

88 Kulkarni AB, Huh C-G, Becker D, Geiser A, Lyght M, Flanders KC *et al.* Transforming growth factor-beta null mutation in mice causes excessive inflammatory response and early death. *Proc Natl Acad Sci U S A* 1993; **90**: 770–4.

89 Ignotz RA, Endo T, Massague J. Regulation of fibronectin and type I collagen mRNA levels by transforming growth factor-beta. *J Biol Chem* 1987; **262**: 6443–6.

90 Edwards DR, Murphy G, Reynolds JJ, Whitham SE, Docherty AJ, Angel P *et al.* Transforming growth factor beta modulates the expression of collagenase and metalloproteinase inhibitor. *EMBO J* 1987; **6**: 1899–904.

91 Laiho M, Saksela O, Keski-Oja J. Transforming growth factor-beta induction of type-1 plasminogen activator inhibitor. Pericellular deposition and sensitivity to exogenous urokinase. *J Biol Chem* 1987; **262**: 17 467–74.

92 Border WA, Noble NA. TGF-β in kidney fibrosis: a target for gene therapy. *Kidney Int* 1997; **51**: 1388–96.

93 Sharma VK, Bologa RM, Xu G-P, Li B, Mouradian J, Wang J *et al.* Intra-graft TGF-β_1 mRNA: a correlate of interstitial fibrosis and chronic allograft nephropathy. *Kidney Int* 1996; **49**: 1297–303.

94 Border WA, Okuda S, Languino LR, Ruoslahti E. Transforming growth factor-beta regulates production of proteoglycans by mesangial cells. *Kidney Int* 1990; **37**: 689–95.

95 Kaneto H, Morrissey J, Klahr S. Increased expression of TGF-beta 1 mRNA in the obstructed kidney of rats with unilateral ureteral ligation. *Kidney Int* 1993; **44**: 313–21.

96 Paul LC, Saito K, Davidoff A, Benediktsson H. Growth factor transcripts in rat renal transplants. *Am J Kidney Dis* 1996; **28**: 441–50.

97 Terrell TG, Working PK, Chow CP, Green JD. Pathology of recombinant human transforming growth factor-β in rats and rabbits. *Int Rev Exp Pathol* 1993; **34**(Part B): 43–67.

98 Shihab FS, Yamamoto T, Nast CC, Cohen AH, Noble NA, Gold LI *et al.* Transforming growth factor-β and matrix protein expression in acute and chronic rejection in human renal allografts. *J Am Soc Nephrol* 1995; **6**: 286–94.

99 Gaciong Z, Koziak K, Religa P, Lisiecka A, Morzycka-Michalik M, Rell K *et al.* Increased expression of growth factors during chronic rejection of human kidney allograft. *Transplant Proc* 1995; **27**: 928–9.

100 Nicholson ML, Bicknell GR, Barker G, Doughman TM, Williams ST, Furness PN. Intragraft expression of transforming growth factor beta 1 gene in isolated glomeruli from human renal transplants. *Br J Surg* 1999; **86**: 1144–8.

101 Cuhaci B, Kumar MS, Bloom RD, Pratt B, Haussman G, Laskow DA *et al.* Transforming growth factor-β levels in human allograft chronic fibrosis correlate with rate of decline in renal function. *Transplantation* 1999; **68**: 785–90.

102 Perrey C, Pravica B, Sinnott JP, Hutchinson IV. Genotyping for polymorphisms in interferon-γ, interleukin-10, transforming growth factor-β_1 and tumour necrosis factor-α genes: a technical report. *Transplant Immunol* 1998; **6**: 193–7.

103 El-Gamel A, Awad MR, Hasleton PS, Yonan NA, Hutchinson JA, Campbell CS *et al.* Transforming growth factor-beta (TGF-beta1) genotype and lung allograft fibrosis. *Heart Lung Transpl* 1999; **18**: 517–23.

104 Dzau VJ. Cell biology and genetics of angiotensin in cardiovascular disease. *J Hypertens* 1994; **12**(Suppl 4): S3–10.

105 Unger T, Gohlke P, Paul M, Rettig R. Tissue renin–angiotensin systems: fact or fiction? *J Cardiovasc Pharmacol* 1991; **18**(Suppl 2): S20–5.

106 Wolf G, Neilson EG. Angiotensin II as a renal growth factor. *J Am Soc Nephrol* 1993; **3**: 1531–40.

107 Unger T, Culman J, Gohlke P. Angiotensin II receptor blockade and end-organ protection: pharmacological rationale and evidence. *J Hypertens* 1998; **16**(Suppl 7): S3–7.

108 Timmermans PBMWN, Wong PC, Chiu AC, Herblin WF, Benfield P, Carini DL *et al.* Angiotensin II receptors and angiotensin II receptor antagonists. *Pharmacol Rev* 1993; **45**: 205–51.

109 Yamada T, Horiuchi M, Dzau VJ. Angiotensin II type 2 receptor mediates programmed cell death. *Proc Natl Acad Sci U S A* 1996; **93**: 156–60.

110 Johnson RJ, Alpers CE, Yoshimura A, Lombardi D, Pritzl P, Floege J *et al.* Renal injury from angiotensin II-mediated hypertension. *Hypertension* 1992; **19**: 464–74.

111 Itoh H, Mukoyama M, Pratt RE, Gibbons GH, Dzau VJ. Multiple autocrine growth factors modulate smooth muscle cell growth response to angiotensin II. *J Clin Invest* 1993; **91**: 2268–74.

112 Kagami S, Border WA, Miller DE, Noble NA. Angiotensin II stimulates extracellular matrix protein synthesis through

induction of transforming growth factor-β expression in rat glomerular mesangial cells. *J Clin Invest* 1994; **93:** 2431–7.

113 Yoshida Y, Kawamura T, Ikomo M, Fogo A, Ichikawa I. Effects of antihypertensive drugs on glomerular morphology. *Kidney Int* 1989; **36:** 626–35.

114 Kakinuma Y, Kawamura T, Bills T, Yoshioka T, Ichikawa I, Fogo A. Blood pressure-independent effect of angiotensin inhibition on vascular lesions of chronic renal failure. *Kidney Int* 1992; **42:** 46–55.

115 Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986; **77:** 1993–2000.

116 Curtis JJ, Luke RG, Whelchel JD, Diethelm AG, Jones P, Dustan HP. Inhibition of angiotensin converting enzyme in renal transplant recipients with hypertension. *N Engl J Med* 1983; **308:** 377–81.

117 Shihab FS, Bennett WM, Tanner AM, Andoh TF. Angiotensin II blockade decreases TGF-β_1 and matrix proteins in cyclosporin nephropathy. *Kidney Int* 1997; **52:** 660–73.

118 Calvino J, Lens XM, Romero R, Sanchez-Guisande D. Long-term anti-proteinuric effects of losartan in renal transplant recipients treated for hypertension. *Nephrol Dial Transplant* 2000; **15:** 82–6.

119 Campistol JM, Inigo P, Jimenez W, Lario S, Clesca PH, Oppenheimer F *et al.* Losartan decreases plasma levels of TGF-β_1 in transplant patients with chronic allograft nephropathy. *Kidney Int* 1999; **56:** 714–19.

120 Kerins DM, Hao Q, Vaughan DE. Angiotensin induction of PAI-1 expression in endothelial cells is mediated by the hexapeptide angiotensin IV. *J Clin Invest* 1995; **96:** 2515–20.

121 Vaughan DE, Lazos SA, Tong K. Angiotensin II regulates the expression of plasminogen activator inhibitor-1 in cultured endothelial cells. A potential link between the renin–angiotensin system and thrombosis. *J Clin Invest* 1995; **95:** 995–1001.

122 Feener EP, Northrup JM, Aiello LP, King GL. Angiotensin II induces plasminogen activator inhibitor-1 and -2 expression in vascular endothelial and smooth muscle cells. *J Clin Invest* 1995; **95:** 1353–62.

123 Fogo AB. The role of angiotensin II and plasminogen activator inhibitor-1 in progressive glomerulosclerosis. *Am J Kidney Dis* 2000; **35:** 179–88.

124 Paul LC. Adverse effects of immunosuppressive drugs on long-term graft outcome. *Transplant Proc* 1998; **30:** 4001–4.

125 Li B, Sehajpal PK, Khanna A, Vlassara H, Cerami A, Stenzel KH *et al.* Differential regulation of transforming growth factor β and interleukin 2 genes in human T cells: demonstration by usage of novel competitor DNA constructs in the quantitative polymerase chain reaction. *J Exp Med* 1991; **174:** 1259–62.

126 Ayanlar-Batuman O, Ferrero AP, Diaz A, Jimenez SA. Regulation of transforming growth factor-β_1 gene expression by glucocorticoids in normal human T lymphocytes. *J Clin Invest* 1991; **88:** 1574–80.

127 Shihab FS. Cyclosporin nephropathy: pathophysiology and clinical impact. *Semin Nephrol* 1996; **16:** 536–47.

128 Palestine AG, Nussenblatt RB, Chan C-C. Side effects of systemic cyclosporine in patients not undergoing transplantation. *Am J Med* 1984; **77:** 652–6.

129 Satterwaite R, Aswad S, Sunga V, Shidban H, Bogaard T, Asai P *et al.* Incidence of new-onset hypercholesterolemia in renal transplant patients treated with FK506 and cyclosporine. *Transplantation* 1998; **65:** 446–9.

130 Copley JB, Staffeld C, Lindberg J, Hansen A, Bailey C, Anand R *et al.* Cyclosporin to tacrolimus: effect on hypertension and lipid profiles in renal allografts. *Transplant Proc* 1998; **30:** 1254–6.

131 Cavaille Coll MW, Elashoff MR. Commentary on a comparison of tacrolimus and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1998; **65:** 142–5.

132 Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. FK506 Kidney Transplant Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1995; **63:** 977–83.

133 Jain S, Bicknell GR, Nicholson ML. Tacrolimus has less fibrogenic potential than cyclosporin A in a model of renal ischaemia–reperfusion injury. *Br J Surg* 2000; **87:** 1563–8.

134 Bicknell GR, Williams ST, Shaw JA, Pringle JH, Furness PN, Nicholson ML. Differential effects of cyclosporin and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants. *Br J Surg* 2000; **87:** 1569–75.

135 Nicholson ML, Bailey E, Williams S, Harris KPF, Furness PN. Computerized histomorphometric assessment of protocol renal transplant biopsy specimens for surrogate markers of chronic rejection. *Transplantation* 1999; **68:** 236–41.

136 Eugui EM, Almquist SJ, Muller CD, Allison AC. Lymphocyte-selective cytostatic and immunosuppressive effects of mycophenolic acid *in vitro*: role of deoxyguanosine nucleotide depletion. *Scand J Immunol* 1991; **33:** 161–73.

137 Allison CA, Eugui EM, Sollinger HW. Mycophenolate mofetil (RS 61443): mechanism of action and effects of in transplantation. *Transplant Rev* 1993; **7:** 129–31.

138 Allison AC, Almquist SJ, Muller CD, Eugui EM. *In vitro* immunosuppressive effects of mycophenolic acid and an ester pro-drug, RS-61443. *Transplant Proc* 1991; **23**(Suppl 2): 10–14.

139 Azuma H, Binder J, Heemann U, Schmid C, Tullius S, Tilney NL. Effects of RS61443 on functional and morphological changes in chronically rejecting rat kidney allografts. *Transplantation* 1995; **59:** 460–6.

140 European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345:** 1321–6.

141 Tricontinental Mycophenolate Mofetil Renal

Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; **61:** 1029–37.

142 Mathew TH. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. *Transplantation* 1998; **65:** 1450–4.

143 Senn B, Rochat P, Schwarkkopf AK, Weinreich T, Binswanger U. Mycophenolate mofetil in ongoing chronic kidney allograft dysfunction. *Transplant Proc* 1998; **30:** 4075–6.

144 Weir MR, Fink JC, Hanes DS, Gardner J, Klassen DK, Cangro C *et al.* Chronic allograft nephropathy: effect of cyclosporin reduction and addition of mycophenolate mofetil on progression of renal disease. *Transplant Proc* 1999; **31:** 1286–7.

145 Fritsche L, Sperschneider H, Budde K, Geissing M, Turk H, Bohler T *et al.* Late conversion to mycophenolate mofetil for chronic deterioration of renal allograft function. *Transplant Proc* 1998; **30:** 2229.

146 Islam MS, Francos GC, Dunn SR, Burke JF. Mycophenolate mofetil and reduction in cyclosporin dosage for chronic renal allograft dysfunction. *Transplant Proc* 1998; **30:** 2230–1.

147 Morris RE. Rapamycins: antifungal, antitumour, antiproliferative, and immunosuppressive macrolides. *Transplant Rev* 1992; **6:** 39.

148 Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998; **31:** 335–40.

149 Mohasci PJ, Tuller D, Hullinger B, Wijngaard PLJ. Different inhibitory effects of immunosuppressive drugs on human and rat aortic smooth muscle and endothelial cell proliferation stimulated by platelet-derived growth factor or endothelial cell growth factor. *J Heart Lung Transplant* 1997; **16:** 484–92.

150 Gregory CR, Pratt RE, Huie P, Shorthouse R, Dzau VJ, Billingham ME *et al.* Effect of treatment with cyclosporin, FK506, rapamycin, mycophenolic acid or deoxyspergualin on vascular smooth muscle proliferation *in vitro* and *in vivo*. *Transplant Proc* 1993; **25:** 770–1.

151 Morris RE, Cao W, Huang X, Gregory CR, Billingham ME, Rowan R *et al.* Rapamycin (sirolimus) inhibits vascular smooth muscle DNA synthesis *in vitro* and suppresses narrowing in arterial allografts and in balloon-injured carotid arteries: evidence that rapamycin antagonizes growth factor action on immune and nonimmune cells. *Transplant Proc* 1995; **27:** 430–1.

152 Stepkowski SM, Kahan BD. Rapamycin and cyclosporine synergistically prolong heart and kidney allograft survival. *Transplant Proc* 1991; **23:** 3262–4.

153 Sacks SH. Rapamycin on trial. *Nephrol Dial Transplant* 1999; **14:** 2087–9.

154 Groth CG, Backman L, Morales JM, Calne R, Kreis H, Lang P *et al.* Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. *Transplantation* 1999; **67:** 1036–42.

155 Kreis H, Cisterne JM, Land W, Wramner L, Squifflet JP, Abramowicz D *et al.* Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000; **69:** 1252–60.

BJS Research Bursary Winners 2001

The total of 91 applications received was the highest ever for *BJS* Research Bursaries. The Council of the *British Journal of Surgery* is delighted to offer awards of £10 000 to the following three surgeons:

Mr Tapan A. Mehta FRCS
Hull Royal Infirmary, Hull, UK
Randomized trial of angioplasty *versus* exercise for intermittent claudication

Miss Claire E. Murphy FRCS
St James' University Hospital, Leeds, UK
Intervention timing and survival in patients with breast cancer

Mr Reyad Al-Ghnaniem MRCS
King's College Hospital, London, UK
Randomized trial of high volume haemofiltration in septic patients

Further details including a list of highly commended entries can be found on the *BJS* website (www.bjs.co.uk).

Jonothan J. Earnshaw
Website Editor

Calcutta University College of Medicine
LIBRARY

Review

Management of thoracic duct injuries after oesophagectomy

S. A. Wemyss-Holden, B. Launois and G. J. Maddern

University of Adelaide Department of Surgery, Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia 5011, Australia
Correspondence to: Professor G. J. Maddern (e-mail: guy.maddern@adelaide.edu.au)

Background: Thoracic duct laceration is a rare but potentially life-threatening complication of oesophagectomy. The management of such an injury is uncertain in respect of the relative merits of conservative and surgical treatment.
Methods: The literature was reviewed by searching Medline databases from 1966 to the present time. The majority of the evidence presented is level 3, as no randomized or controlled data are available.
Results: Prolonged conservative treatment of thoracic duct injury is associated with a mortality rate of 50–82 per cent. The results of early surgical ligation of the duct are more encouraging, with a mortality rate of 10–16 per cent. Elective ligation of the duct reduces the incidence of postoperative chylothorax.
Conclusion: The thoracic duct should be ligated during oesophagectomy. A high index of suspicion for duct injury must be maintained in all patients after operation. A policy of very early thoracic duct ligation at 48 h from diagnosis is proposed for duct injury if aggressive conservative management fails.

Paper accepted 26 June 2001

British Journal of Surgery 2001, **88**, 1442–1448

Introduction

The thoracic duct was first described in a horse by Eustachius, a Roman anatomist, in 1565. However, it was not until some 69 years later that Veslingus described the duct in humans[1]. Chylothorax was first described by Bartolet in 1633[2] and in 1875 Quincke reported chylothorax resulting from thoracic trauma[3]. It was not until 1936, however, that this entity was first reported as a complication of thoracic surgery[4], albeit in an experimental setting. In 1953 Bressler *et al.*[5] reported chylothorax complicating oesophageal surgery. Peet and Campbell[6] in 1943 were the first to describe ligation of the duct for chylothorax. Unfortunately the patient died rapidly, from an unknown cause, in the peroperative period. However, in 1948 Lampson[7] successfully ligated the duct following its traumatic disruption. Before this the mortality rate from conservative management of duct injury was close to 50 per cent[8].

Iatrogenic damage to the thoracic duct is now a well recognized, albeit rare, complication of thoracic surgery and particularly of oesophagectomy. The incidence of such injury after oesophagectomy varies from 0·2 to 10·5 per cent[9–16], although most series report an incidence of around 3 per cent. The incidence also varies according to the operative procedure. Transhiatal[12] and thoracoscopic[17] resection appears to be associated with an increased risk of duct laceration. It is also well documented that the duct can be damaged as a result of cardiothoracic surgery[18], blunt thoracic trauma[19,20], penetrating thoracic injuries[21,22], neck trauma[23,24], neck surgery[25,26], spinal fractures[27,28] and even radical nephrectomy[29]. Even with modern supportive and operative methods of treatment, the mortality rate in these patients is close to 30 per cent[30–32].

Anatomy and physiology

If damage to the thoracic duct is to be avoided during oesophagectomy or if the duct is to be repaired surgically, it is essential that the operator has an accurate understanding of its anatomical course. The thoracic duct is the main collecting channel of the lymphatic system and resembles a large vein histologically. It is formed in the midline at the level of the second lumbar vertebra at the cisterna chyli. It passes cephalad through the diaphragmatic hiatus and ascends through the chest on the right side of the thoracic spine. At the level of the fourth thoracic vertebra, the duct crosses to the left side of the chest and continues its course along the left side of the oesophagus. In the root of the neck, it arches forward and laterally to emerge between the left subclavian and common carotid arteries. It then passes between the internal jugular vein and the scalenus anterior muscle to join the left subclavian vein at the angle it makes with the left internal jugular vein[33]. Although this is the classical course, variations are common and include lymphatic and lymphaticovenous anastomoses, duplication of ducts, multiple cross channels and even a completely right-sided system[34]; the classic duct occurs in only about half the population.

In a normal adult, the thoracic duct transports up to 4 litres of chyle each day, but the flow rate is influenced by several factors, including gut function, diet, drug intake and the degree of mobility. The flow of chyle is maintained within the duct by changes in intra-abdominal and intrathoracic pressures (respiration, coughing, etc.), transmitted compression from large adjacent arteries and contraction of the duct's own muscular wall[35]. Almost all chyle originates from the liver and gastrointestinal tract[36] and so contains not only high concentrations of the products of digestion but also lymphocytes and immunoglobulins[35]. Some 60–70 per cent of dietary fat enters the systemic circulation via the thoracic duct, and lymphocytes (of which 90 per cent are T cells) constitute 95 per cent of the cellular component of chyle. The concentrations of electrolytes, antibodies and enzymes approximate to those of plasma[37–40]. Chyle contains between 4 and 59 g fat, and 22–59 g protein per litre, depending on dietary intake[41].

Persistent leakage from the thoracic duct of chyle, rich in fluid, electrolytes, lipid, protein and lymphocytes, poses a difficult clinical management problem for the surgeon or intensivist. The patient, already debilitated by virtue of disease, premorbid condition and postoperative catabolic state, becomes progressively nutritionally and immune deficient as leakage continues[35,42]. With prolonged leakage, total body reserves of protein, albumin, fat and vitamins become depleted. Importantly, continued loss of electrolytes results in acidosis, hyponatraemia and hypocalcaemia[43]. In addition, the ongoing loss of lymphocytes, antibodies and albumin increases the risk of bacterial and viral sepsis[44], and it is interesting to note that elective drainage of the thoracic duct was proposed in the precyclosporin era as a possible means of improving graft survival after renal transplantation[45–47]. Such uncontrolled losses undoubtedly account for the 50 per cent mortality rate that was observed before surgical ligation of the duct was introduced[8] and modern-day supportive therapies became available. Indeed, the prolonged period of recovery described in quite recent studies in which conservative management was advocated[41,48,49] may also be explained by this ongoing loss.

Mechanism of injury and clinical presentation

Laceration of the thoracic duct during oesophagectomy, whether performed via the transthoracic, transhiatal or thoracoscopic route, must be regarded as a technical failure. An injury sustained at open surgery is likely to result from a direct, inadvertent incision or transection of the duct; it is difficult to visualize and is often never positively identified. During transhiatal resection, however, the mechanism of injury is different, involving tearing and shear forces[49] while the surgeon blindly mobilizes the distal oesophagus which may be adherent to adjacent soft tissues. This explains the relatively high incidence of duct injury during this procedure[12]. As is usual with endoscopic procedures, the surgeon's visual appreciation and interpretation of the operative field is limited by several factors during thoracoscopic mobilization of the oesophagus. In the context of duct injury, the most relevant factors include lack of three-dimensional vision and a magnification effect[17]. Thoracoscopic oesophagectomy is still in its relative infancy but early reports suggest that it may be associated with a high incidence of duct laceration[17]. The mechanisms described above can produce two distinct types of injury. First, the duct may be transected or partially resected with the operative specimen and there is then no chance of it healing with conservative treatment. Second, a small lateral branch of the duct may be damaged, or a small laceration may occur; in these situations the duct may heal with conservative treatment. Unfortunately, there is no way of differentiating accurately between these two types of injury.

Laceration of the thoracic duct usually presents in the early postoperative period as an excessive drainage (more than 500 ml) of straw-[12] or cream-coloured fluid from the chest drain (or abdominal drain after transhiatal resection). However, there is often a refractory period of 2–10 days between the time of surgical injury and the appearance of chyle in the chest drain. It is presumed that this results from early, occult leakage into the mediastinum that later discharges into the pleural cavity[20] and chest drain. If no chest drain is inserted at the time of surgery (as after transhiatal resection), the local accumulation of chyle in the pleural cavity may lead to progressive mediastinal shift, with compression of the contralateral lung and reduced cardiac function[14]. Standard posteroanterior chest radiographs may be of value in confirming the diagnosis. The appearance is either normal if the chyle is draining or one of a large mediastinal shadow if the pleura is intact[5].

Delay in the diagnosis of postoperative duct injury must be avoided if the potentially fatal complications of persistent chyle loss are to be averted. However, the diagnosis is often difficult to make in the early postoperative period when drainage of straw-coloured fluid is a normal occurrence. If this drainage does not rapidly reduce in volume within 24–48 h, or becomes milky in appearance, then thoracic duct laceration should be suspected and investigated. Administration of a fatty fluid such as cream[10,32] via an enteral feeding tube may confirm the diagnosis if the chyle changes to a milky appearance. Alternatively, dyes such as methylene blue or Sudan III have been used in a similar way[50], but they are not specific for thoracic duct injury. Laboratory analysis of the fluid may also reveal high concentrations of lymphocytes and lipids[32]. In particular, the presence of chylomicrons (using electrophoresis) is diagnostic of chyle[9,35,51].

Management of thoracic duct injury after oesophagectomy

Controversy surrounds the need for accurate preoperative localization of the site of duct injury. If the surgeon intends to *repair* a laceration in the duct, identification of its location is imperative for preoperative planning. If, however, the intention is to *ligate* the duct above the diaphragm, identifying the site of injury is unimportant and imaging is not routinely required. In situations of repair, the imaging modality should not only demonstrate the presence of leakage but also identify accurately the precise site of injury.

Controversy has surrounded the management of thoracic duct injury since it was first described. Before the advent of surgical ligation[6,7], when supportive measures were extremely limited, the mortality rate approached 50 per cent[8]. However, the development of modern medical therapy and surgical technique has dramatically increased the therapeutic options available to the clinician. Several different strategies have evolved, ranging from the purely conservative, through combined conservative/surgical, to early aggressive surgical repair or ligation.

The authors believe that it is the nature of the thoracic duct as a conduit that results in delayed healing after injury and hence the controversy surrounding the appropriate management. In some ways the thoracic duct may be likened to the bile duct. It is a relatively large-calibre and fragile conduit with a minimally contractile wall which relays fluid with no constituents capable of occluding a defect in its wall, unlike a blood vessel. It seems probable, therefore, that any laceration to the duct will be associated with fistula formation and a prolonged repair process.

Conservative management

An experimental study in dogs has demonstrated that iatrogenic injury to the thoracic duct heals spontaneously in 5–10 days, depending on whether the conduit is lacerated or transected[52]. However, this study was performed in young, healthy animals without malignancy and this may explain why such rapid healing is not commonly observed in the clinical setting. It does show, however, that the duct has the potential for repair with non-operative treatment and it is recognized that in humans very small tears may well heal spontaneously. Nevertheless, as the volume of chyle leakage increases, so the chance of resolution declines. Indeed, it has recently been demonstrated that the volume of chyle drainage on the fifth day after operation predicts the chances of success with continued medical management; if the drainage is less than 10 ml per kg body-weight per day the chance of success is high[53]. The principles of conservative treatment of thoracic duct injury include reduction of chyle flow, drainage of the pleural cavity, nutritional support and prevention of septic complications[14]. When such a management strategy is instigated, surgical repair is often considered only after a prolonged period over which it gradually becomes clear that conservative treatment has failed.

The flow of chyle can be reduced by a factor of 10 by avoiding enteral feeding containing fat[54]. Octreotide may reduce chyle flow[55–57] but this notion is controversial[58]. Etilefrine, a sympathomimetic drug that causes smooth muscle contraction, has also been advocated recently but the evidence is limited to a case report[59]. It is essential that the pleural cavity is drained adequately such that chyle does not accumulate as the development of a 'chyloma' prevents the lung from expanding fully. This not only compromises respiratory function but also prevents effective 'plugging' of the defect in the thoracic duct by the visceral pleura. If it is suspected that the chest drain is blocked, it should be replaced. If the patient has undergone transhiatal resection and chyle accumulates, a separate chest drain should be inserted in addition to the abdominal drain.

If conservative treatment is to be successful, enteral or parenteral nutrition should be started as soon as the diagnosis of injury has been made. Enteral nutrition offers the potential advantage of preventing bacterial translocation but the normal lipid content of the feed increases chyle flow. However, medium-chain triglycerides are transported directly into the portal venous system[60] and enteral feeds rich in these have been shown to reduce the duration of chylothorax[61]. Long-term use of such a diet may result in linoleic acid deficiency as this essential fatty acid is found only in long-chain triglycerides[44]. Despite the theoretical advantage of feeding via the enteral route, many studies reporting on conservative management of thoracic duct injury advocate the use of total parenteral nutrition and fasting[10,44,62–64]. A randomized clinical trial is needed to answer the question of the preferred route for the administration of nutritional support. It is unlikely, however, that this trial will ever take place owing to the relative rarity of the condition.

An interesting new idea is to collect the chyle from the chest drain and reinfuse it back into the patient with the aim of reducing the immunological and metabolic consequences of prolonged chyle leakage[20]. This novel concept requires further evaluation. Because of impaired immune function, patients should be examined regularly for signs of infection, not only of the surgical wound and site of chyle drainage but also of the respiratory and urinary tracts. Patients with duct injury are at risk of death from overwhelming bacterial and fungal sepsis[30].

The mortality rate when conservative management is used as the mainstay of treatment is not well reported, but in one study it was nearly 50 per cent[12]. In this study of 11 patients, four were treated successfully, four died during conservative treatment, and three underwent surgical repair after 10 days of unsuccessful conservative treatment, of whom one died. Similarly, Milsom *et al.*[31] reported death in five of six patients treated conservatively. Orringer *et al.*[10] concluded that 'traditional conservative management of a chylothorax with chest tube drainage, intravenous hyperalimentation, and no or low-residue enteral feedings has little place in patients who have been operated on for oesophageal obstruction due to either benign or malignant disease'. In the light of such apparent failure of prolonged conservative treatment, there is a consensus that continuation (more than 2 weeks) of such treatment should be avoided and surgical repair should be undertaken to prevent the situation becoming unsalvageable[10,30,31,65].

Surgical management

Injury may occur to the thoracic duct anywhere along its course from the diaphragm to the root of the neck. If the surgeon intends to close the defect, identification of its location is imperative for an appropriate surgical approach to be planned. Lymphoscintigraphy[66–71], lymphangiography[72–75] and, more recently, computed tomgraphy (CT)[75–77] have all been used to image duct injury.

Although lymphoscintigraphy may be helpful in selected cases[71,78], its routine use cannot be supported. As with all techniques involving the use of radioisotopes, this method poses logistical problems, particularly for patients who may be ventilated in the intensive care unit. The radioisotopes may need to be prepared specially or obtained from a remote centre. The patient needs to be transported repeatedly to the γ-camera for up to 24 h, and the resulting images are often of relatively low resolution and unhelpful in determining the exact location of the leak.

Lymphangiography involves the subcutaneous injection of an oily contrast medium such as ethiodol[73] or lipiodol[74] into each foot. Plain chest radiographs are then performed to detect any leakage of contrast agent from the duct. In situations of injury, contrast agent is usually seen in the mediastinum after about 45 min[73]. The exact site of the laceration can be identified reliably[73], allowing accurate preoperative planning[74,75].

It has been suggested that CT may have a role in imaging duct injury[75–77], with[76] or without the use of ingested ethiodized oil. However, Sachs *et al.*[75] evaluated the relative merits of lymphangiography and CT in 12 patients with suspected postoperative duct injury and concluded that 'Laceration of the thoracic duct was accurately diagnosed and localized with lymphangiography, which allowed definitive surgical repair. CT was of little additional value in diagnosing these injuries'. Still, CT may have a limited application in patients who present late, in whom there are concerns about tumour recurrence[14]. Based on this evidence, it is suggested that if a postoesophagectomy duct laceration is suspected and the surgeon is planning on repair (as opposed to ligation), the patient should undergo urgent lymphangiography. CT has no place as a first-line investigation.

Even during surgical re-exploration it is sometimes extremely difficult to locate the injury. The lung may be stiff and difficult to collapse. The pleura is thickened and the gastric tube largely fills the posterior mediastinum. Remobilization risks damaging the integrity of the oesophagogastric anastomosis and the laceration itself may be extremely small and difficult to see. The site of damage can usually be identified if a bolus of cream is given via a nasogastric or nasojejunal tube. Milky fluid drips from the laceration at a rate of one to two drops every second[14]. Methylene blue may also be used[79] but this often results in unwanted staining of other structures in the chest and provides little additional information[41]. It has been suggested that parietal pleurectomy should be performed if the exact site of leakage cannot be identified[44].

Any laceration is usually repaired with a suture but the thoracic duct is very fragile and the stitch may tear out with consequent persistence of the chyle leak. An alternative is the use of a vascular clip[80] and, more recently, the application of fibrin glue has been reported, with encouraging results, either at thoracotomy[81,82] or thoracoscopy[83].

Because of the technical problems associated with identifying and repairing lacerations, supradiaphragmatic ligation of the duct has been proposed. The preferred method is to ligate the duct '*en bloc*' between the aorta and the vertebral bodies just above the diaphragmatic hiatus. Since the first surgical ligations described by Peet and Campbell[6] and Lampson[7], such ligation has involved a thoracotomy. However, the advent of endoscopic surgery has made thoracoscopic ligation possible[80,84,85]; this may reduce postoperative pain and morbidity compared with open operation. The collective results of open duct ligation are good, with successful ligation reported in approximately 95 per cent of patients with minimal additional morbidity[13,35,41,86,87]. Milsom *et al.*[31] have reported a mortality rate of only 16 per cent after ligation, compared with 82 per cent after conservative management.

Some surgeons favour elective duct ligation at the time of the initial operation to prevent postoperative chylothorax[9]. Dougenis *et al.*[13] reported a marked reduction in overt duct injury (2 *versus* 9 per cent) when the duct was ligated electively. *En bloc* oesophagectomy[16,88] with extended lymphadenectomy (two or three field) by definition includes excision of the thoracic duct with ligation of the proximal and distal ends, and may reduce the incidence of a chyle leak.

A new management protocol

Fortunately thoracic injury is a relatively rare complication of oesophagectomy. This, in turn, means that the evidence base from which to formulate a management plan is small. However, based on this review of the available literature and the experience of the senior authors, a new management strategy for postoesophagectomy duct injury will be presented. It is important to appreciate that this strategy is for a duct that has been surgically lacerated during oesophagectomy; the following aggressive schema should be applied only to this situation and not to chylothorax of alternate aetiology.

Although there is little clear evidence to support its routine use, the authors believe that the duct should be positively identified and carefully mass ligated as a routine part of oesophagectomy. This strategy remains controversial, however, as the thoracic duct may actually be damaged as a part of the ligation process, thereby leading to a postoperative leak. If this policy is to be adopted, then the duct should be carefully ligated '*en bloc*' in the angle between the aorta and the vertebral bodies as close to the diaphragm as is technically feasible.

A high index of suspicion of duct injury should be maintained by the surgeon and intensivist in all patients who have undergone oesophagectomy. If after 24 h there is any increase in volume or colouration of the chest/abdominal drain fluid, a sample of the fluid should be examined for the presence of lymphocytes and chylomicrons. The authors believe that the use of cream or lipophilic dyes is neither a sensitive nor specific test of thoracic duct injury. Their use may delay diagnosis and so should be avoided. If the drainage fluid is found to contain high levels of lymphocytes and chylomicrons (and is therefore chyle), a defined period of 48–72 h of aggressive conservative treatment should be started. Routine imaging to determine the site of injury is unnecessary if the duct is to be ligated (not repaired). The patient should be rendered nil-by-mouth, all enteral feeding stopped and total parenteral nutrition administered via a central venous catheter. During this time exact fluid and electrolyte balance must be maintained, and an accurate measure of the *hourly* drainage of chyle should be recorded and charted graphically.

After 48–72 h of conservative treatment a full reassessment is made. If at that time the volume of chyle drainage remains above 10 ml per kg body-weight per 24 h, there is probably little chance of spontaneous resolution and the patient should undergo urgent duct ligation. This may be performed either by reopening the existing surgical wound or thoracoscopically, if the facilities and expertise are available. The duct must be identified and carefully mass ligated just above the diaphragm. Only if there has been a marked reduction in the rate of chyle drainage should conservative treatment be continued; even then, reassessment is required every 24 h. If the drainage has not stopped completely after 1 week, urgent ligation should be performed.

This aggressive policy of early ligation of the thoracic duct depends on an early postoperative 'window of opportunity'. Over the first 72 h after surgery, most patients remain relatively fit, without the debilitation of weeks or months of failed conservative treatment. By adopting the policy of routine thoracic ligation during oesophagectomy and early duct ligation if postoperative chyle leakage occurs, the authors believe that the mortality rate will be reduced.

References

1 O'Neill JN. Ligation of thoracic duct for chylothorax due to blunt trauma. Case report. *Am Surg* 1965; **31:** 757–8.

2 Bower GC. Chylothorax: observations in 20 cases. *Dis Chest* 1964; **46:** 464–8.

3 Quincke H. Weberfetthaltige Transsudate – Hydrops chylosua adioposus. *Dtsch Arch Klin Med* 1875; **16:** 121.

4 Blalock A, Cunningham RS, Robinson CS. Experimental production of chylothorax by occlusion of the superior vena cava. *Ann Surg* 1936; **104:** 359–64.

5 Bressler S, Wiener D, Thompson SA. Traumatic chylothorax following esophageal resection. *J Thorac Surg* 1953; **26:** 321–4.

6 Peet MM, Campbell KN. Massive chylothorax following splanchnicectomy. *Ann Arbor* 1943; **9:** 2.

7 Lampson RS. Traumatic chylothorax. Review of literature and report of a case treated by mediastinal ligation of the thoracic duct. *J Thorac Surg* 1948; **17:** 778–91.

8 Zakhour BJ, Drucker MH, Franco AA. Chylothorax as a complication of aortocoronary bypass. Two case reports and a review of the literature. *Scand J Thorac Cardiovasc Surg* 1988; **22:** 93–5.

9 Lam KH, Lim ST, Wong J, Ong GB. Chylothorax following resection of the oesophagus. *Br J Surg* 1979; **66:** 105–9.

10 Orringer MB, Bluett M, Deeb GM. Aggressive treatment of chylothorax complicating transhiatal esophagectomy without thoracotomy. *Surgery* 1988; **104:** 720–6.

11 Collard JM, Otte JB, Reynaert M, Michel L, Carlier MA, Kestens PJ. Esophageal resection and by-pass: a 6 year experience with a low postoperative mortality. *World J Surg* 1991; **15:** 635–41.

12 Bolger C, Walsh TN, Tanner WA, Keeling P, Hennessy TP. Chylothorax after oesophagectomy. *Br J Surg* 1991; **78**: 587–8.

13 Dougenis D, Walker WS, Cameron EW, Walbaum PR. Management of chylothorax complicating extensive esophageal resection. *Surg Gynecol Obstet* 1992; **174**: 501–6.

14 Merrigan BA, Winter DC, O'Sullivan GC. Chylothorax. *Br J Surg* 1997; **84**: 15–20.

15 Hankins JR, Miller JE, Attar S, Mclaughlin JS. Transhiatal esophagectomy for carcinoma of the esophagus: experience with 26 patients. *Ann Thorac Surg* 1987; **44**: 123–7.

16 Skinner DB. *En bloc* resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1983; **85**: 59–71.

17 Takemura M, Osugi H, Tokuhara T, Kinoshita H, Higashino M. Chylothorax after thoracoscopic esophagectomy. *Jpn J Thorac Cardiovasc Surg* 2000; **48**: 238–41.

18 Cevese PG, Vecchioni R, D'Amico DF, Cordiano C, Biasiato R, Favia G *et al.* Postoperative chylothorax. Six cases in 2500 operations, with a survey of the world literature. *J Thorac Cardiovasc Surg* 1975; **69**: 966–71.

19 O'Neill JN. Ligation of thoracic duct for chylothorax due to blunt trauma. Case report. *Am Surg* 1965; **31**: 757–8.

20 Montebugnoli M, Borghi B, Bugamelli B, Righi V, Boaron DM, Valbonesi M *et al.* Salvage and reinfusion of chyle in closed chest injury. *Int J Artif Organs* 1998; **21**: 235–9.

21 Worthington MG, de Groot M, Gunning AJ, von Oppell UO. Isolated thoracic duct injury after penetrating chest trauma. *Ann Thorac Surg* 1995; **60**: 272–4.

22 von Oppell UO, Bautz P, De Groot M. Penetrating thoracic injuries: what we have learnt. *Thorac Cardiovasc Surg* 2000; **48**: 55–61.

23 Allen SJ, Koch SM, Tonnesen AS, Bowman-Howard M, Khalil K. Tracheal compression caused by traumatic thoracic duct leak. *Chest* 1994; **106**: 296–7.

24 Whiteford MH, Abdullah F, Vernick JJ, Rabinovici R. Thoracic duct injury in penetrating neck trauma. *Am Surg* 1995; **61**: 1072–5.

25 Spiro JD, Spiro RH, Strong EW. The management of chyle fistula. *Laryngoscope* 1990; **100**: 771–4.

26 Seelig MH, Klingler PJ, Oldenburg WA. Treatment of a postoperative cervical chylous lymphocele by percutaneous sclerosing with povidone–iodine. *J Vasc Surg* 1998; **27**: 1148–51.

27 Gartside R, Hebert JC. Chylothorax following fracture of the thoracolumbar spine. *Injury* 1988; **19**: 363–4.

28 Nagai H, Shimizu K, Shikata J, Iida H, Matsushita M, Ido K *et al.* Chylous leakage after circumferential thoracolumbar fusion for correction of kyphosis resulting from fracture. Report of three cases. *Spine* 1997, **22**: 2766–9.

29 Cespedes RD, Peretsman SJ, Harris MJ. Chylothorax as a complication of radical nephrectomy. *J Urol* 1993; **150**: 1895–7.

30 Ferguson MK, Little AG, Skinner DB. Current concepts in the management of postoperative chylothorax. *Ann Thorac Surg* 1985; **40**: 542–5.

31 Milsom JW, Kron IL, Rheuban KS, Rodgers BM. Chylothorax: an assessment of current surgical management. *J Thorac Cardiovasc Surg* 1985; **89**: 221–7.

32 Marts BC, Naunheim KS, Fiore AC, Pennington DG. Conservative *versus* surgical management of chylothorax. *Am J Surg* 1992; **164**: 532–4(discussion 534–5).

33 Stubbs WK, Tabb HG. Thoracic duct injuries. *South Med J* 1977; **70**: 1062–3.

34 Kausel HW, Reeve TS, Stein AA, Alley RD, Stranahan A. Anatomic and pathologic studies of the thoracic duct. *J Thorac Surg* 1957; **34**: 631–41.

35 Paes ML, Powell H. Chylothorax: an update. *Br J Hosp Med* 1994; **51**: 482–90.

36 Yoffey JM, Courtice FC. *Lymphatics, Lymph and Lymphoid Tissue.* London: Edward Arnold, 1956.

37 Birt AB, Connolly NK. Traumatic chylothorax: a report of a case and a survey of the literature. *Br J Surg* 1952; **39**: 564–8.

38 Seaman JB. Rationale and a new technique in traumatic cylothorax with report of a case. *J Thorac Surg* 1954; **27**: 529–39.

39 Stringel G, Mercer S, Bass J. Surgical management of persistent postoperative chylothorax in children. *Can J Surg* 1984, **27**: 543–6.

40 Shafiroff BGP, Kau QY. Cannulation of the human thoracic lymph duct. *Surgery* 1959; **45**: 814–9.

41 Robinson CL. The management of chylothorax. *Ann Thorac Surg* 1985; **39**: 90–5.

42 Breaux JR, Marks C. Chylothorax causing reversible T-cell depletion. *J Trauma* 1988, **28**: 705–7.

43 Servelle M, Nogues C, Soulie J, Andrieux JB, Terhedebrugge R. Spontaneous, post-operative and traumatic chylothorax. *J Cardiovasc Surg (Torino)* 1980; **21**: 475–86.

44 Puntis JW, Roberts KD, Handy D. How should chylothorax be managed? *Arch Dis Child* 1987; **62**: 593–6.

45 Starzl TE, Weil R III, Koep LJ, McCalmon RT, Terasaki PI, Iwaki Y *et al.* Thoracic duct fistula and renal transplantation. *Ann Surg* 1979; **190**: 474–86.

46 Machleder HI, Paulus H. Clinical and immunological alterations observed in patients undergoing long-term thoracic duct drainage. *Surgery* 1978; **84**: 157–65.

47 Fish JC, Sarles HE, Remmers A, Townsend CM, Bell JD, Flye MW. Renal transplantation after thoracic duct drainage. *Ann Surg* 1981; **193**: 752–6.

48 Macfarlane JR, Holman CW. Chylothorax. *Am Rev Respir Dis* 1972; **105**: 287–91.

49 Valentine VG, Raffini TA. The management of chylothorax. *Chest* 1992; **102**: 586–91.

50 Theaker NJ, Brady PW, Fisher MM. Postesophagectomy mediastinal chylothorax causing upper airway obstruction misdiagnosed as asthma: a report of two cases. *Chest* 1997; **111**: 1126–8.

51 Seriff NS, Cohen ML, Samuel P, Schulster PL. Chylothorax: diagnosis by lipoprotein electrophoresis of serum and pleural fluid. *Thorax* 1977; **32**: 98–100.

52 Hodges CC, Fossum TW, Evering W. Evaluation of thoracic duct healing after experimental laceration and transection. *Vet Surg* 1993; **22**: 431–5.

53 Dugue L, Sauvanet A, Farges O, Goharin A, Le Mee J, Belghiti J. Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy. *Br J Surg* 1998; **85:** 1147–9.

54 Co TUI, Barcham IS, Chafiroff BGP. Ligation of the thoracic duct and the posthemorrhage plasma protein level. *Surg Gynecol Obstet* 1944; **79:** 37–40.

55 Ulibarri JI, Sanz Y, Fuentes C, Mancha A, Aramendia M, Sanchez S. Reduction of lymphorrhagia from ruptured thoracic duct by somatostatin. *Lancet* 1990; **335:** 258.

56 Pelizzo MR, Toniato A, Piotto A, Bernante P. Somatostatin in the treatment of lymphorrhea after lateral neck dissection. *Minerva Chir* 1992; **47:** 1485–7.

57 Markham KM, Glover JL, Welsh RJ, Lucas RJ, Bendick PJ. Octreotide in the treatment of thoracic duct injuries. *Am Surg* 2000; **66:** 1165–7.

58 Van Gossum A, Stefanidis C, De Franquen P. Lack of effect of somatostatin and analogues in lymphorrhagia from ruptured thoracic duct. *Lancet* 1992; **339:** 491–2.

59 Guillem P, Billeret V, Houcke ML, Triboulet JP. Successful management of post-esophagectomy chylothorax/chyloperitoneum by etilefrine. *Dis Esophagus* 1999; **12:** 155–6.

60 Senior JR. The place of medium chain triglycerides. *Am J Med Sci* 1969; **257:** 75–80.

61 Jalili F. Medium-chain triglycerides and total parenteral nutrition in the management of infants with congenital chylothorax. *South Med J* 1987; **80:** 1290–3.

62 Bessone LN, Ferguson TB, Burford TH. Chylothorax. *Ann Thorac Surg* 1971; **12:** 527–50.

63 Sassoon CS, Light RW. Chylothorax and pseudochylothorax. *Clin Chest Med* 1985; **6:** 163–71.

64 Light RW. *Pleural Diseases*. 2nd ed. Philadelphia, Pennsylvania: Lea & Febiger, 1990.

65 Selle JG, Snyder WH III, Schreiber JT. Chylothorax: indications for surgery. *Ann Surg* 1973; **177:** 245–9.

66 Gates GF, Dore EK, Kanchanapoom V. Thoracic duct leakage in neonatal chylothorax visualized by 198 Au lymphangiography. *Radiology* 1972; **105:** 619–20.

67 Woolfenden JM, Struse TB. Diagnosis of chylothorax with ^{131}I-triolein: case report. *J Nucl Med* 1977; **18:** 128–9.

68 Mine H, Tamura K, Tanegashima K, Shinozaki Y. Non-traumatic chylothorax associated with diffuse lymphatic dysplasia. *Lymphology* 1984; **17:** 111–12.

69 Baulieu F, Baulieu JL, Alison D, Barsotti J, Itti R. Use of lymphscintigraphy in traumatic chylous ascites. *Lymphology* 1987; **20:** 93–5.

70 Baulieu F, Baulieu JL, Mesny J, Ducouret N, Benhamov AC, Barsotti J *et al.* Visualization of the thoracic duct by lymphoscintigraphy. *Eur J Nucl Med* 1987; **13:** 264–5.

71 Moadel-Sernick RM, Crooke GA, Freeman LM. Lymphoscintigraphy demonstrating thoracic duct injury in an infant with hypoplastic left heart syndrome. *Clin Nucl Med* 2000; **25:** 335–6.

72 Heilman RD, Collins VP. Identification of laceration of the thoracic duct by lymphangiography. *Radiology* 1963; **81:** 470–2.

73 Chavez CM, Conn JH. Thoracic duct laceration. Closure under conservative management based on lymphangiography evaluation. *J Thorac Cardiovasc Surg* 1966; **51:** 724–8.

74 Ngan H, Fok M, Wong J. The role of lymphography in chylothorax following thoracic surgery. *Br J Radiol* 1988; **61:** 1032–6.

75 Sachs PB, Zelch MG, Rice TW, Geisinger MA, Risius B, Lammert GK. Diagnosis and localization of laceration of the thoracic duct: usefulness of lymphangiography and CT. *AJR Am J Roentgenol* 1991; **157:** 703–5.

76 Day DL, Warwick WJ. Thoracic duct opacification for CT scanning. *AJR Am J Roentgenol* 1985; **144:** 403–4.

77 Watanabe AT, Jeffrey RB. CT diagnosis of traumatic rupture of the cisterna chyli. *J Comput Assist Tomogr* 1987; **11:** 175–6.

78 Rice TW, Kirsh JC, Schacter IB, Goldberg M. Simultaneous occurrence of chylothorax and subarachnoid pleural fistula after thoracotomy. *Can J Surg* 1987; **30:** 256–8.

79 Engevik L. Traumatic chylothorax. *Scand J Thorac Cardiovasc Surg* 1976; **10:** 77–8.

80 Crosthwaite GL, Joypaul BV, Cuschieri A. Thoracoscopic management of thoracic duct injury. *J R Coll Surg Edinb* 1995; **40:** 303–4.

81 Stenzl W, Rigler B, Tscheliessnigg KH, Beitzke A, Metzler H. Treatment of postsurgical chylothorax with fibrin glue. *Thorac Cardiovasc Surg* 1983; **31:** 35–6.

82 Akaogi E, Mitsui K, Sohara Y, Endo S, Ishikawa S, Hori M. Treatment of postoperative chylothorax with intrapleural fibrin glue. *Ann Thorac Surg* 1989; **48:** 116–18.

83 Inderbitzi RG, Krebs T, Stirneman T, Ulrich A. Treatment of postoperative chylothorax by fibrin glue application under thoracoscopic view with use of local anesthesia. *J Thorac Cardiovasc Surg* 1992; **104:** 209–10.

84 Janssen JP, Joosten HJ, Postmus PE. Thoracoscopic treatment of postoperative chylothorax after coronary bypass surgery. *Thorax* 1994; **49:** 1273.

85 Kent RB III, Pinson TW. Thoracoscopic ligation of the thoracic duct. *Surg Endosc* 1993; **7:** 52–3.

86 Patterson GA, Todd TR, Delarue NC, Ilves R, Pearson FG, Cooper JD. Supradiaphragmatic ligation of the thoracic duct in intractable chylous fistula. *Ann Thorac Surg* 1981; **32:** 44–9.

87 Miyamura H, Watanabe H, Eguchi S, Suzuki T. Ligation of the thoracic duct through transabdominal phrenotomy for chylothorax after heart operations. *J Thorac Cardiovasc Surg* 1994; **107:** 316.

88 Peracchia A, Fumagalli U, Segalin A, Bonavina L. Congress issue – state of the art: pathogenesis, diagnosis and treatment of cancer of the tubular oesophagus. *Dis Esophagus* 1995; **8:** 167–74.

Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy

Y.-H. Ho, F. Seow-Choen, C. Tsang and K.-W. Eu

Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608
Correspondence to: Dr Y.-H. Ho (e-mail: HoYH@sgh.gov.sg)

Background: Conventional stapled haemorrhoidectomy involves the use of a large circular anal dilator (DL technique), which may cause anal sphincter injuries. This study compared whether the procedure can be effectively performed without this dilator (ND technique), with better sphincter preservation.
Methods: Fifty-eight patients with symptomatic prolapsed irreducible haemorrhoids were randomized to DL ($n = 29$) and ND ($n = 29$) groups. Preoperative continence scoring, anorectal manometry and endoanal ultrasonography were performed. These were repeated at up to 14 weeks after operation, with additional pain scores, analgesic requirements and quality of life assessments.
Results: DL haemorrhoidectomy took significantly longer to perform ($P = 0{\cdot}02$). However, there were fewer residual skin tags ($P = 0{\cdot}044$) and less perianal pruritis ($P = 0{\cdot}007$) at 2 weeks, although such symptoms subsided to an equivalent level in both groups afterwards. Internal anal sphincter fragmentation persisting to at least 14 weeks was found in four patients after DL, but not after ND haemorrhoidectomy ($P = 0{\cdot}038$). However, these were asymptomatic and no differences were found in continence scores and anal pressures. The pain scores, satisfaction scores, quality of life assessments and time off work were similar.
Conclusion: The large circular anal dilator used for stapled haemorrhoidectomy increased the risk of anal sphincter injuries, which may become problematic with ageing.

Paper accepted 20 June 2001

British Journal of Surgery 2001, 88, 1449–1455

Introduction

There has been recent enthusiasm over the novelty of stapled haemorrhoidectomy. Pescatori *et al.*[1] described the transanal introduction of a circular intraluminal stapling device to excise redundant rectal mucosa. Longo[2] refined the technique to aim at stapling interruption of the feeding superior haemorrhoidal arteries, above the base of the haemorrhoids. Excessive prolapsed mucosa was drawn back into the anal canal to be excised in the stapler doughnut and to be fixed in place by the stapled anastomosis. Residual external haemorrhoidal skin tags that could not be entirely drawn into the anus would shrivel and become asymptomatic[2,3]. Essential to the technique was the absence of sensitive perianal wounds. Randomized clinical studies have since shown reduced postoperative pain and an earlier return to work[3–5]. The hospital stay may be shortened[4], but the substantial added cost of the single-use stapling instrument could not be recovered by any of the above advantages[3]. There is also a risk of persistent postoperative pain[6] and a rare chance of pelvic sepsis[7].

There has also been concern that the use of a stapling instrument in stapled haemorrhoidectomy may result in incontinence[6,8]. Impaired anal pressures and endoanal ultrasonographic evidence of internal anal sphincter defects have been reported after the transanal introduction of stapling devices for colorectal cancer surgery[9–11]. However, randomized data have shown that the continence score, and anorectal manometric and endoanal ultrasonographic findings are no different from those after open haemorrhoidectomy[3]. None the less, most surgeons experienced with conventional stapled haemorrhoidectomy would be concerned about the use of a large-diameter circular anal dilator for insertion of the purse-string and through which the intraluminal stapler is introduced (DL technique; *Fig. 1*). In fact, an Eisenhammer retractor may be used effectively to insert the purse-string and the intraluminal stapler may be introduced directly into the anal canal (ND technique). This avoids unnecessary stretching of the anal sphincters. This report describes a randomized controlled trial designed to compare DL with ND haemorrhoidectomy. The endpoints studied were continence scoring,

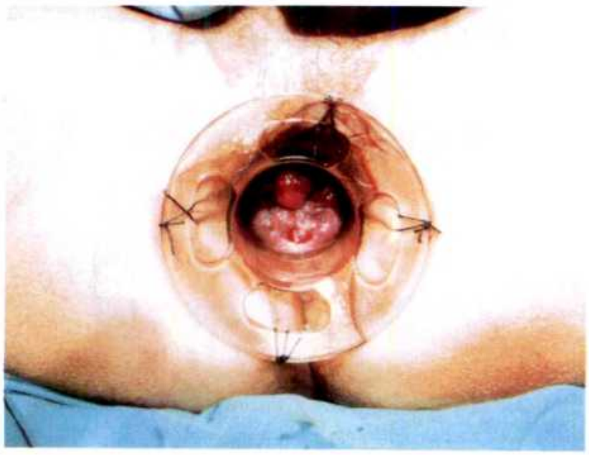


Fig. 1 Technique of stapled haemorrhoidectomy using an anal dilator. A circular anal dilator (37 mm external diameter) is inserted into the anus and secured with sutures to the skin

anorectal manometry, endoanal ultrasonographic findings, as well as clinical outcomes including pain, complications, quality of life and time taken off work.

Patients and methods

Patients

Following approval by the hospital ethics committee, consecutively consenting patients with symptomatic prolapsed irreducible haemorrhoids were recruited. Exclusion criteria were patients with previous perianal surgery, acutely thrombosed internal haemorrhoids and bleeding disorders. Colonoscopy was performed before operation for patients over the age of 50 years, with recent changes in bowel habit, mucus in the stools or a family history of colorectal cancer. All other patients underwent rigid sigmoidoscopy to exclude other pathology in the anus and rectum. Group allocation was by computerized randomization.

Surgical technique

Surgery was performed under general anaesthesia, with the patient in the lithotomy position. Both DL and ND techniques were standardized according to protocol, and the times taken for the operation were recorded.

DL stapled haemorrhoidectomy was performed using the PPH set (procedure for prolapsed haemorrhoids; Ethicon Endo-surgery, Cincinnati, Ohio, USA). This consisted of a circular anal dilator (37 mm external diameter), purse-string anoscope, suture threader and a 33-mm haemorrhoidal circular stapler. The circular anal dilator was gently inserted into the anus and secured with sutures to the skin (*Fig. 1*). Its obturator was removed and replaced with the purse-string anoscope. The gap in the anoscope was rotated around the anus for application of a 2/0 polypropylene purse-string suture. This stitch included submucosal bites of the lower rectum, at least 2 cm above the dentate line. The anoscope was removed and the opened haemorrhoidal circular stapler was inserted so that its distal anvil was beyond the purse-string suture. The purse-string suture was then firmly tied. Its free ends were brought through the hollow shoulder of the haemorrhoidal circular stapler and out through one of the side-holes situated more proximally, using the suture threader. Thus, traction upon this purse-string as the circular stapler was being closed enabled loose anorectal mucosa distal to the purse-string to be pulled proximally into the hollowed shoulder of the stapler, and to be included in the excised doughnut. After firing of the stapler, the jaws were kept closed for approximately 2 min, for haemostasis. The jaws were then opened slightly to free the stapler from surrounding tissues and removed together with the circular dilator.

In the ND technique, the circular dilator and purse-string anoscope were not used. Instead, an Eisenhammer retractor was gently opened intermittently to a maximum of 3 cm to enable insertion of the purse-string suture. The haemorrhoidal stapler was applied directly, so the maximum anal dilatation was limited to the diameter of the stapling gun itself.

After operation, patients in both groups were prescribed fibre supplements and ketoprofen 100-mg tablets or intramuscular pethidine 1 mg per kg body-weight. Patients without complications were offered hospital discharge on the day of surgery, but could elect to stay overnight if apprehensive about wound care.

Data collection

Before operation patients were assessed with a faecal continence score, anorectal manometry and endoanal ultrasonography. Before discharge from hospital, blinded observers assessed linear analogue pain scores, patient satisfaction and analgesic requirements. At 2 weeks after discharge, the patients were reviewed clinically. Blinded observers also reassessed the pain score, patient satisfaction and analgesic requirements. At 6 weeks after surgery, assessment consisted of clinical review, continence scoring, anorectal manometry and endoanal ultrasonography. At 14 weeks after surgery, the above were repeated and a quality of life questionnaire was also administered.

The faecal continence score employed has been described previously and is well accepted in use[12]. Anorectal

Table 1 Pain score, analgesic requirements and satisfaction after stapled haemorrhoidectomy

	In hospital		After 2 weeks		After 6 weeks		After 14 weeks	
	DL	ND	DL	ND	DL	ND	DL	ND
Maximum pain*†	4·1(0·6)	4·9(0·5)	3·4(0·7)	2·3(0·5)	–	–	–	–
Pain at bowel movement*†	4·0(0·8)	3·7(1·1)	2·0(0·5)	3·0(0·6)	–	–	–	–
Pethidine injections required (1 mg per kg body-weight)*	0·2(0·1)	0·2(0·0)	–	–	–	–	–	–
Ketoprofen requirement (no. of 100-mg tablets)*	1·8(0·2)	2·1(0·1)	6·5(1·9)	10·6(1·7)	0	2·4(2·2)	0·1(0·1)	0·1(0·0)
No. of patients with residual pain	–	–	–	–	3	6	0	5
Satisfaction*‡	7·6(0·2)	7·0(0·4)	7·5(0·3)	6·9(0·4)	–	–	–	–

*Values are mean(s.e.). Stapled haemorrhoidectomy was carried out with (DL) and without (ND) use of an anal dilator for insertion of the purse-string suture (29 patients in each group). †Pain linear analogue score ranged from 0 (no pain) to 10 (comparable to worse pain ever experienced); ‡satisfaction linear analogue score ranged from 0 (totally dissatisfied) to 10 (completely satisfied). There were no significant differences between DL and ND operations

manometry was performed as described previously[13], using a microcapillary perfusion system (Synectics, Stockholm, Sweden). An experienced sonographer performed endoanal ultrasonography, using a Leopard 2001™ scanning system with a 10-MHz endoanal probe (B&K Medical, Standtoffen, Denmark). Another experienced sonographer, who was blinded to the randomization, confirmed all findings on the printed images. The validated Eypasch Gastrointestinal Quality of Life instrument[14] was used to assess quality of life.

Values are given as mean(s.e.) unless otherwise indicated. Statistical analysis was performed using the SPSS/PC+ package (SPSS, Chicago, Illinois, USA). χ^2 and Mann–Whitney tests were used to test for statistical significance, as appropriate. Power calculations suggested that approximately 60 patients would be needed to identify a 10 per cent reduction in ultrasonographic defects with a power of 80 per cent at the 5 per cent significance level.

Results

There were 29 patients in each group, and there were no significant differences in age, gender and clinical features. In the DL group, there were 12 men and the mean age was 42·5(1·7) years. The symptoms were bleeding in 24 patients, prolapse in 22, pain in 11 and pruritis in seven. Mean number of bowel movements per week was 7·8(1·2) and symptom duration was 3·4(1·3) years. To date, follow-up has been for 7·4(0·3) months. In the ND group, there were 14 men and the mean age was 46·3(2·1) years. The symptoms were bleeding in 25 patients, prolapse in 23, pain in 13 and pruritis in 11. Mean number of bowel movements per week was 11·3(2·5), and mean symptom duration was 3·6(1·0) years. To date, follow-up has been for 7·2(0·3) months. The patients' compliance with medication was lowest at 14 weeks after surgery, but there were no differences between the DL ($n = 23$) and ND ($n = 16$) groups.

Apart from the intraoperative times, there were no significant differences encountered during the hospital stay. DL haemorrhoidectomy took longer to perform (17·8(1·4) *versus* 12·7(0·9) min; $P = 0{\cdot}02$). The stapling doughnuts were intact and complete in all patients. Postoperative stay was 1·9(0·1) days after DL haemorrhoidectomy and 2·0(0·1) days after the ND operation. Six patients in the DL group and four in the ND group had opened their bowels before discharge.

There were no differences in pain scores, analgesic requirements and satisfaction scores between the two groups at 2, 6 and 14 weeks after surgery (*Table 1*). The residual pain in both groups at 6 and 14 weeks was mild, and analgesic requirements were minimal. Perianal pruritis and complaints of residual external skin tags were significantly more common in the ND group at 2 weeks (*Table 2*). The pruritis and skin tags subsequently resolved in most patients in both groups.

The total complications were no different after DL ($n = 8$) and ND ($n = 9$) operations. Mild stenosis was the most common complication (six patients in each group). All stenoses occurred in patients who were non-compliant to fibre supplements, and were usually detected at 6 weeks after surgery. They were soft and easily dilated digitally in the clinic, without analgesia. All but two in the ND group had responded to a single dilatation and fibre supplements by 14 weeks. The recalcitrant stenoses were found to be substantially firmer by then and required dilatation under

Table 2 Postoperative wound condition after stapled haemorrhoidectomy

	After 2 weeks		After 6 weeks		After 14 weeks	
	DL	ND	DL	ND	DL	ND
Residual minor rectal bleeding	8	8	4	4	1	3
Symptomatic residual skin tags	4	12†	4	3	1	2
Perianal pruritis	4	15‡	7	5	4	8
Anal discharge	6	2	1	1	0	2
Bowel movements per week*	12·6(1·5)	10·7(1·3)	8·9(0·9)	9·3(0·8)	9·2(0·9)	9·0(1·3)

*Values are mean(s.e.). Stapled haemorrhoidectomy was carried out with (DL) and without (ND) use of an anal dilator for insertion of the purse-string suture (29 patients in each group). †$P = 0·044$, ‡$P = 0·007$ *versus* DL (χ^2 test)

Table 3 Anorectal manometric and endoanal ultrasonographic findings after stapled haemorrhoidectomy

	Before surgery		After 6 weeks		After 14 weeks	
	DL	ND	DL	ND	DL	ND
Continence score (0–24)[12]*	0·1(0·0)	0·01(0·0)	0·0(0·0)	0·2(0·2)	0·1(0·1)	0·0(0·0)
Mean resting anal pressure (mmHg)*	62·1(4·3)	57·3(5·2)	53·3(3·9)	44·9(4·1)	49·2(3·5)	42·9(3·0)
Maximum anal squeeze pressure (mmHg)*	200·8(13)	220·4(16·9)	204·1(18·3)	208·5(16·7)	170·8(11·5)	119·8(18·3)
Physiological anal length (cm)*	2·0(0·2)	1·8(0·3)	1·9(0·2)	1·6(1·8)	1·9(0·2)	1·6(0·1)
Internal anal sphincter thickness (mm)*	2·3(0·1)	2·2(0·1)	2·2(0·1)	2·3(0·1)	2·4(0·1)	2·3(0·1)
Internal anal sphincter fragmentation	0	0	4	0†	4	0†
External anal sphincter thickness (mm)*	9·7(0·5)	9·9(0·5)	10·2(0·3)	9·5(0·3)	9·5(0·4)	9·1(0·4)
External anal sphincter fragmentation	0	0	0	0	0	0

*Values are mean(s.e.). Stapled haemorrhoidectomy was carried out with (DL) and without (ND) use of an anal dilator for insertion of the purse-string suture (29 patients in each group). †$P = 0·038$ *versus* DL (χ^2 test)

general anaesthesia. None have recurred to date. Bleeding occurred in one patient after DL haemorrhoidectomy before discharge from hospital and led to readmission after 7 days in one patient in the ND group. Both were treated successfully by submucosal adrenaline injection[15]. Faecal impaction requiring a phosphate enema occurred in one patient in each group. The remaining complication was urinary retention requiring catheterization in one patient after ND haemorrhoidectomy. No haemorrhoids have yet recurred.

Stapled haemorrhoidectomy did not affect the continence scores and there was no difference in scores between the two groups (*Table 3*). Before surgery, two patients in the DL group were occasionally incontinent to gas. One of them also stained her underwear rarely with liquid stool. One patient in the DL group was occasionally incontinent to gas. The postoperative continence scores reflected the symptoms in these three patients. No other patient had continence affected by either of the techniques. Anorectal manometric findings were unchanged after surgery, and no differences were found between DL and ND groups. However, endoanal ultrasonography showed new internal anal sphincter defects (*Figs 2* and *3*) in four patients after DL haemorrhoidectomy but none after the ND operation ($P = 0·038$). None of the patients with a sphincter defect had symptoms of incontinence.

There were no differences between groups in the time taken off work and quality of life scores. The time taken to resume full working duties or normal life style in housewives and retirees was 17(2) and 21(2) days after DL and ND operations respectively. There were no differences in either the total or individual-component Eypasch Gastrointestinal Quality of Life scores between the groups (DL: symptoms 69·3(1·4), emotions 18·8(0·5), physical function 26·5(0·7), social functions 12·3(0·9), total score 130·9(2·5); ND: symptoms 66·7(2·1), emotions 18·3(0·6), physical function 25·3(0·7), social functions 12·8(0·7), total score 127(3·5)).

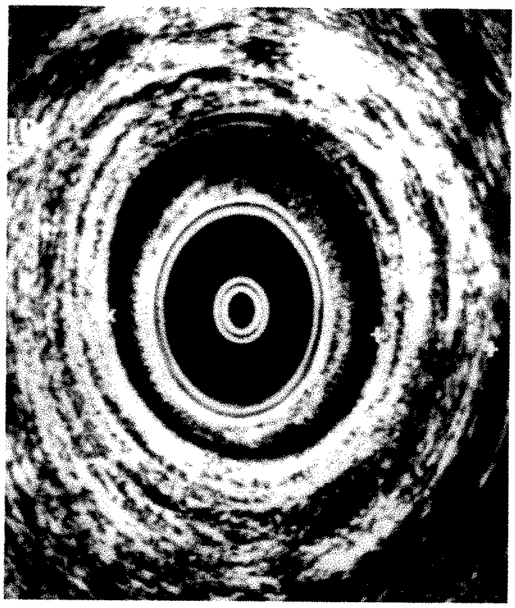


Fig. 2 Preoperative endoanal ultrasonography showed intact anal sphincters at the midanal canal level. (Anterior of patient is at 12 o'clock position)

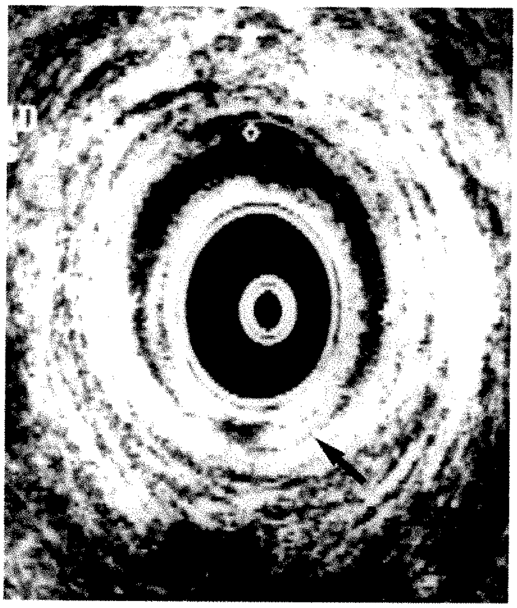


Fig. 3 Postoperative endoanal ultrasonography at 14 weeks showed fragmentation of the internal anal sphincter (arrow), in the same patient and at approximately the same level. (Anterior of patient is at 12 o'clock position)

Discussion

There was endoanal ultrasonographic evidence of internal anal sphincter fragmentation in four of 29 patients after DL, but none after ND haemorrhoidectomy. In both groups, a 33-mm circular intraluminal stapler was inserted into the anus. Transanal introduction of stapling devices has been shown to result in internal anal sphincter injuries[9–11]. Other forms of transanal surgery such as excision of rectal tumours[16] and rectocele repair[17,18] have also been found to result in impaired anal pressures. However, with the DL technique the 37-mm external diameter circular anal dilator (included in the PPH set) was inserted into the anus for almost the entire duration of the procedure. With the ND technique, the Eisenhammer retractor was opened only intermittently to a maximum of 3 cm for purse-string insertion. Furthermore, the circular dilator distended the anal canal all over its circumference, whereas the Eisenhammer retractor stretched in only one direction. There were no other differences between the DL and ND techniques. It is likely that the more extensive and prolonged anal dilatation with the DL technique increased the risk of anal sphincter injury.

None the less, none of the patients with anal sphincter injuries were symptomatic. The changes in continence scores and the manometric findings following both techniques of stapled haemorrhoidectomy were no different. Asymptomatic internal anal sphincter injuries have been reported previously after stapled haemorrhoidectomy[3], transanal surgery[18] and transanal stapling gun insertion[9]. Incontinence may have been averted by adequate compensation from reserves in the anal sphincter muscles, especially in relatively young patients. In addition, good rectal reservoir function may compensate for weakened anal sphincters after anterior resection[19,20]. However, these well compensated but persistent injuries (at least up to 14 weeks) may potentially become problematic with the onset of ageing.

Apart from the above, the DL technique took longer to perform (required the added step of stitching the dilator to the skin and was also usually ergonometrically less efficient than the ND procedure for purse-string placement) but resulted in fewer anal skin tags and less perianal pruritis at 2 weeks. It is likely that the use of the circular anal dilator facilitated reduction of the prolapsed haemorrhoidal components into the anal canal. This would make it easier to excise the excessive loose mucosa in the stapler doughnut and to fix the prolapsing tissues in place by the stapled anastomosis[2]. None the less, from 6 weeks onwards, the residual external skin tags that could not be entirely drawn into the anus shrivelled such that there were no longer any differences between the DL and ND groups, in line with previously reported experience[2,3]. In fact, none of the residual skin tags that remained at 14 weeks caused any concern to patients in either group. It is difficult to explain the transient perianal pruritis at 2 weeks, especially in the ND group. There was no statistical association between the pruritis and residual skin tags.

The lack of any differences in pain, satisfaction scores, postoperative quality of life and time taken off work were not surprising, as both techniques of stapled haemorrhoidectomy were similar, except for the sphincter defects resulting from the former. It was not unexpected that anal sphincter compromise did not affect the postoperative pain. It has previously been shown that neither lateral internal sphincterotomy[21] nor pharmacological reduction in anal sphincter tone[22] significantly affected postoperative pain. Although some patients had residual pain up to 14 weeks after surgery, the pain was minimal and easily controlled with analgesics. All such pain had resolved well before 7 months' final follow-up. Persistent pain and faecal urgency, which have both been reported previously after stapled haemorrhoidectomy[6], were not found[3]. The complication rates were similar in the two study groups. Although there has been a case report of pelvic sepsis after stapled haemorrhoidectomy[7], this was not encountered in the present series.

It is conceded that operator dependency and possible false identification of anal sphincter injury at endoanal ultrasonography is possible[23]. None the less, endosonography was performed by an experienced endosonographer who was blinded to the randomization. Another experienced sonographer, who was unaware of the original findings, confirmed the findings on printed images. Larger patient numbers would possibly have made the results more conclusive by overcoming the variability in manometric measurements to provide a significant correlation with the endoanal ultrasonographic findings.

Use of a circular dilator for inserting the purse-string during stapled haemorrhoidectomy causes unnecessary stretching of the anal canal. This may be avoided by inserting the purse-string through an intermittently and gently opened Eisenhammer retractor. However, the circular dilator may provide better reduction of prolapsed piles into the anal canal, resulting in fewer residual skin tags in the early postoperative period, although such excessive skin tags tend to shrivel a few weeks later, probably as the result of the superior haemorrhoidal vessel branches being stapled off. Surgeons should be aware of possible stretch injuries to the anal sphincters and due care should be exercised during haemorrhoidectomy, including the stapled technique.

References

1 Pescatori M, Favetta U, Dedola S, Orsini S. Transanal stapled excision of rectal mucosa prolapse. *Techniques in Coloproctology* 1997; **1:** 96–8.

2 Longo A. Treament of hemorrhoidal disease by reduction of mucosa and hemorrhoidal prolapse with a circular suturing device: a new procedure. In: *Proceedings of the 6th World Congress of Endoscopic Surgery*. Bologna: Monduzzi Edotore, 1998: 777–94.

3 Ho Y-H, Cheong W-K, Tsang C, Ho J, Eu K-W, Tang C-L *et al.* Stapled hemorrhoidectomy – cost and effectiveness. Randomized, controlled trial including incontinence scoring, anorectal manometry, and endoanal ultrasound assessments at up to three months. *Dis Colon Rectum* 2000; **43:** 1666–75.

4 Mehigan BJ, Monson JRT, Hartley JE. Stapling procedure for haemorrhoids *versus* Milligan–Morgan haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355:** 782–5.

5 Rowsell M, Bello M, Hemingway DM. Circumferential mucosectomy (stapled haemorrhoidectomy) *versus* conventional haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355:** 779–81.

6 Cheetham MJ, Mortensen NJ, Nystrom PO, Kamm MA, Phillips RK. Persistent pain and faecal urgency after stapled haemorrhoidectomy. *Lancet* 2000; **356:** 730–3.

7 Molloy RG, Kingsmore D. Life threatening pelvic sepsis after stapled haemorrhoidectomy. *Lancet* 2000; **355:** 810.

8 Fazio VW. Early promise of stapling technique for haemorrhoidectomy. *Lancet* 2000; **355:** 768–9.

9 Ho Y-H, Tsang C, Tang CL, Nyam D, Eu KW, Seow-Choen F. Anal sphincter injuries from stapling instruments introduced transanally: randomized, controlled study with endoanal ultrasound and anorectal manometry. *Dis Colon Rectum* 2000; **43:** 169–73.

10 Farouk R, Duthie GS, Lee PWR, Monson JRT. Endosonographic evidence of injury to the internal anal sphincter after low anterior resection: long-term follow-up. *Dis Colon Rectum* 1998; **41:** 888–91.

11 Ho Y-H, Tan M, Leong A, Eu KW, Nyam D, Seow-Choen F. Anal sphincter function impaired after stapler insertion for colorectal anastomosis: a randomized, controlled trial. *Dis Colon Rectum* 1999; **42:** 89–95.

12 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; **36:** 77–97.

13 Ho Y-H, Seow-Choen F, Goh HS. Haemorrhoidectomy and disordered rectal and anal physiology in patients with prolapsed haemorrhoids. *Br J Surg* 1995; **82:** 596–8.

14 Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling CS, Neugebauer E *et al.* Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995; **82:** 216–22.

15 Nyam DCNK, Seow-Choen F, Ho Y-H. Submucosal adrenaline injection for posthemorrhoidectomy hemorrhage. *Dis Colon Rectum* 1995; **38:** 776–7.

16 Keck JO, Schoetz DJ Jr, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC. Rectal mucosectomy in the treatment of giant rectal villous tumors. *Dis Colon Rectum* 1995; **38:** 233–8.

17 Arnold MW, Stewart WR, Aguilar PS. Rectocele repair. Four years' experience. *Dis Colon Rectum* 1990; **33:** 684–7.

18 Ho Y-H, Ang M, Nyam D, Tan M, Seow-Choen R. Transanal approach to rectocele repair may compromise anal sphincter pressures. *Dis Colon Rectum* 1998, **41**: 354–8.

19 Ho Y-H, Wong J, Goh HS. Level of anastomosis and anorectal manometry in predicting function following anterior resection for adenocarcinoma. *Int J Colorectal Dis* 1993; **8**: 170–4.

20 Speakman CT, Burnett SJ, Kamm MA, Bartram CI. Sphincter injury after anal dilatation demonstrated by anal endosonography. *Br J Surg* 1991; **78**: 1429–30.

21 Mathai V, Ong BC, Ho Y-H. Randomized controlled trial of lateral internal sphincterotomy with haemorrhoidectomy. *Br J Surg* 1996; **83**: 380–2.

22 Ho Y-H, Seow-Choen F, Low JY, Tan M, Leong APKF. Randomized controlled trial of trimebutine (anal sphincter relaxant) for pain after haemorrhoidectomy. *Br J Surg* 1997; **84**: 377–9.

23 Sentovich SM, Blatchford GJ, Rivela LJ, Lin K, Thorson AG, Christensen MA. Diagnosing anal sphincter injury with transanal ultrasound and manometry. *Dis Colon Rectum* 1997; **40**: 1430–4.

Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy

C. Gouillat*, J. Chipponi†, J. Baulieux‡, C. Partensky§, J. Saric¶ and B. Gayet**

Department of Surgery, *Hôtel Dieu, ‡Hôpital de la Croix-Rousse, §Hôpital Edouard Herriot, Lyon, †Hôtel Dieu, Clermont-Ferrand, ¶Hôpital St André, Bordeaux and **Institut Mutualiste Montsouris, Paris, France

Correspondence to: Professor C. Gouillat, Department of Surgery, Hôtel Dieu, 1 place de l'Hôpital, 69288 Lyon Cedex 02, France (e-mail: christian.gouillat@chu-lyon.fr)

Background: It remains debatable whether somatostatin can prevent pancreatic fistula and other pancreatic stump-related complications following pancreaticoduodenectomy. This study assessed the effects of somatostatin-14 (S-14) on pancreatic remnant exocrine secretion.

Methods: This was a double-blind, randomized, placebo-controlled trial in patients undergoing pancreaticoduodenectomy for malignancy. Patients received a continuous infusion of S-14 ($n = 38$) or placebo ($n = 37$) for 7 days. Pancreatic juice and peripancreatic drainage fluid was collected and measured, and pancreatic enzymes were monitored daily. Postoperative complications were recorded.

Results: S-14 infusion was associated with a decrease in median daily pancreatic juice and pancreatic amylase output. Amylase concentration and output in the peripancreatic drain fluid were significantly lower after S-14 infusion than in the control group (both $P < 0.05$). The incidence of clinical pancreatic fistula (two of 38 *versus* eight of 37; $P < 0.05$) and total pancreatic stump-related complications (five of 38 *versus* 12 of 37; $P < 0.05$) was lower in patients treated with S-14. Duration of hospital stay was shorter after S-14 (18 *versus* 26 days; $P = 0.01$).

Conclusion: Although the effect of S-14 on exocrine secretion remains difficult to demonstrate, it did reduce pancreatic juice leakage from the pancreatic remnant.

Paper accepted 26 June 2001

British Journal of Surgery 2001, **88**, 1456–1462

Introduction

Despite advances in surgical techniques and progress in intensive care, the morbidity rate following pancreaticoduodenectomy remains as high as 30–50 per cent[1–3]. Major complications, such as pancreatic fistula, intra-abdominal fluid collection and postoperative pancreatitis, are chiefly associated with the soft consistency of the pancreatic remnant and the consequent exocrine secretion[2,4,5]. There is general agreement that pancreatic stump-related complications are usually due to pancreatic juice leakage from the pancreatic remnant[6].

Somatostatin-14 (S-14) and its analogues have well recognized inhibitory effects on exocrine pancreatic secretion[7] and could reduce the risk of complications following pancreatic surgery. Four European randomized multicentre clinical trials have reported a reduction in the overall incidence of complications in patients receiving octreotide, a synthetic long-acting somatostatin analogue[8–11], and meta-analysis of these trials has suggested that the use of octreotide is a cost-effective strategy[3]. Two additional smaller, non-placebo-controlled randomized studies support these findings[12,13]. Despite the positive results of these studies, they failed to demonstrate conclusively the benefit of using octreotide to prevent pancreatic fistula and other pancreatic stump-related complications in patients undergoing pancreaticoduodenectomy for malignancy and/or with a soft, normal pancreas, both of which are considered risk factors for complications[14]. Two randomized single-centre trials from North America found no benefit in using octreotide[14,15]. Further data on the prophylactic use of somatostatin are limited to a few small open studies[16–18].

The aim of this pilot trial was to assess the effects of S-14, which is identical to the native hormone, on pancreatic remnant exocrine secretion and related morbidity in patients undergoing pancreaticoduodenectomy for malignancy.

Patients and methods

Study design

The study was designed as a multicentre, double-blind, placebo-controlled, randomized trial; patients were enrolled at eight French academic surgical centres. Informed written consent was obtained from each patient and the appropriate ethics committees approved the study protocol.

Patients

Patients aged 18–75 years who needed pancreaticoduodenectomy for presumed tumour, without evidence of chronic pancreatitis on preoperative imaging, were eligible for inclusion in the study. Patients with a known allergy to somatostatin or mannitol, and those who had received somatostatin or analogues within 3 days of surgery, were excluded. Preoperative radiation therapy was not employed. Randomization was done using a list balanced in blocks of four in each centre at the time of surgery, after the feasibility of pancreatectomy had been confirmed and eligibility criteria satisfied.

Surgical procedure

Pancreatic anastomosis was performed according to the routine procedure employed by each surgeon, but included a pancreatic tube to facilitate collection of pancreatic juice. During the first 7 days after operation patients received total parenteral nutrition and continuous infusion of either S-14 (Somatostatine®; UCB Pharma, Nanterre, France) at a dose of 6 mg per 24 h (days 1–6) and 3 mg per 24 h (day 7), or matching placebo (mannitol 4 mg).

Pancreatic juice diversion

Exocrine secretion from the pancreatic remnant was assessed using a simple pancreatic juice diversion system. A tube containing distal side holes, the same diameter as the pancreatic duct to ensure a secure fit, was inserted in the pancreatic duct at the time of construction of the pancreatic anastomosis (pancreaticojejunostomy or pancreaticogastrostomy according to the surgeon's choice)[19]. The opening of the tube was connected to a collecting bottle on the floor to facilitate gravitational drainage. At least one other drain was placed in the vicinity of the pancreatic anastomosis.

The volume of pancreatic juice and abdominal drainage fluid, together with their amylase and lipase concentrations, was monitored daily for 12 days after surgery. Total daily amylase and lipase output was calculated by multiplying the concentration of enzyme by the volume collected in 24 h.

The pancreatic tube remained in the pancreatic duct until 12 days after surgery. The peripancreatic drains were removed after 5 days when normal amylase concentration was demonstrated in the drainage fluid.

Assessments and definitions

In addition to monitoring pancreatic juice and drain fluid, patients were assessed daily using standard clinical and biological variables (including amylase and lipase serum concentrations) for 12 days after surgery. All adverse events were recorded. When necessary additional investigations, including computed tomography (CT), were performed.

A *clinical* pancreatic fistula was defined as the drainage (more than 100 ml/day) of amylase-rich drainage fluid (greater than five times the upper limit of normal for serum amylase) after day 3, persisting after day 12 or in association with raised temperature (above 38°C) or other symptoms requiring further surgery, percutaneous drainage or transfer to intensive care. A *biochemical* pancreatic fistula was defined as an asymptomatic fistula, identified by raised amylase concentrations in the drainage fluid (more than five times the upper limit of normal for serum amylase) after day 3, for 5 days or more, but which resolved spontaneously before day 12.

The following complications were considered to be potentially related to pancreatic juice leaks (other pancreatic stump-related complications): intra-abdominal infected fluid collection revealed by ultrasonography, CT, guided needle aspiration or further surgery; or acute pancreatitis, defined as an increase to at least three times the normal plasma amylase concentration more than 4 days after operation, associated with morphological signs using contrast-enhanced CT.

Total pancreatic stump-related complications included clinical pancreatic fistula and other pancreatic stump-related complications. Other abdominal complications that required further surgery, percutaneous drainage or transfer to the intensive care unit were also recorded, as was death in hospital or within 30 days of discharge. Overall complications included all the above-mentioned events.

Postoperative complications were recorded for all patients enrolled in the trial. In contrast, analysis of pancreatic secretions included only evaluable patients for whom a measurable, totally clear (no bile contamination), volume of fluid collected from the pancreatic tube was available and who completed the entire protocol. Analysis of enzyme concentrations in the peripancreatic drainage fluid was performed only for evaluable patients for whom a measurable volume of collected fluid was available.

Statistical analysis

The primary endpoint for statistical analysis was reduction in pancreatic juice output. Secondary endpoints were amylase and lipase output in the pancreatic juice, amylase and lipase concentrations and output in the drainage fluid, incidence of clinical pancreatic fistula and total pancreatic stump-related complications, and duration of postoperative hospital stay.

The *a priori* primary hypothesis, based on experience of pancreatic juice diversion[3] and predicted effects of S-14, was that somatostatin infusion would decrease the mean pancreatic juice output from 200 to 50 ml per 24 h. It was calculated that 24 evaluable patients were required in each group with α and β errors each of 5 per cent (95 per cent power). To ensure an adequate number of patients for all analyses the trial aimed to recruit a minimum of 35 patients to each treatment arm.

Data are presented by incidence, percentage, median, mean(s.e.m.), minimum and maximum. For statistical analysis, all tests used were two tailed with a significance level of 5 per cent. Qualitative variables were compared using χ^2 test, or Fisher's exact test when the expected cell counts were below five. For quantitative variables (pancreatic juice output, enzyme concentrations and outputs), intergroup differences were evaluated using repeated-measures analysis of variance (ANOVA) as the primary analysis. Intragroup variation was evaluated using a non-parametric test (Friedman rank test).

Results

Patients

Between October 1995 and December 1996, 75 patients were recruited into the study and randomized to receive either S-14 ($n = 38$) or placebo (mannitol; $n = 37$). The demographics of the two groups were similar, particularly with respect to pancreatic remnant consistency, mean pancreatic duct diameter and anastomotic technique employed (*Table 1*).

Eight patients (six receiving S-14 and two placebo; $P = 0{\cdot}26$) did not complete the study. Reasons included major violation of the protocol with regard to surgical procedure or administrative modalities ($n = 2$), three possible S-14-related complications (attack of delirium, bradycardia and septicaemia) and early further surgery or death ($n = 3$).

Pancreatic juice collected from the pancreatic tube

Forty-eight patients (64 per cent) were evaluable (S-14, $n = 23$; placebo, $n = 25$). Important differences were observed between patients with respect to both pancreatic juice output and enzyme concentration.

Table 1 Demographics of 75 patients who underwent pancreaticoduodenectomy

	Somatostatin (*n* = 38)	Placebo (*n* = 37)
Age (years)*	58·5(2·0)	62·0(1·8)
Sex ratio (M : F)	25 : 13	26 : 11
ASA grade†		
I	14	17
II	20	13
III	2	5
Diagnostic pathology		
Adenocarcinoma	32	29
Other tumours	6	4
Chronic pancreatitis	0	4
Pancreatic remnant consistency		
Soft	30	34
Intermediate	8	2
Hard	0	1
Pancreatic duct diameter (mm)*	3·9(0·4)	4·0(0·4)
Anastomotic technique		
Pancreaticojejunostomy	24	27
Pancreaticogastrostomy	14	10
Pylorus preservation	18	19

*Values are mean(s.e.m.). †Data missing for four patients. ASA, American Society of Anesthesiologists

Pancreatic juice output

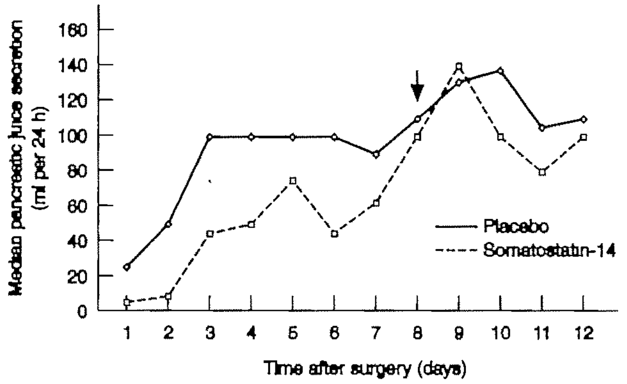
Compared with placebo, S-14 infusion was associated with a lower median pancreatic juice output in the first 7 days, followed by an increase to a value comparable to that observed in the control group (*Fig. 1a*). Mean daily output increased gradually between days 1 and 7 after operation (S-14, $P < 0{\cdot}01$; placebo, $P < 0{\cdot}01$) (*Fig. 1b*); however, ANOVA failed to demonstrate a significant difference between treated and control groups ($P = 0{\cdot}52$).

Amylase and lipase output

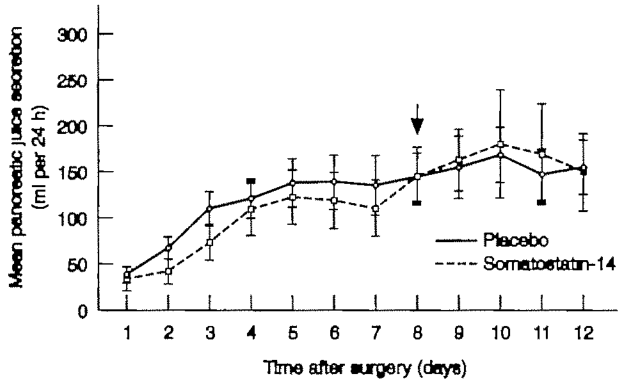
ANOVA failed to demonstrate any significant difference between the S-14-treated and control groups in amylase and lipase output ($P = 0{\cdot}32$). However, during the S-14 infusion (postoperative days 1–7), the median amylase output was typically lower than that in the control group and stopping S-14 infusion was associated with an increase in amylase output (*Fig. 2a*). A notable variability in lipase output was observed in the control group. In contrast, in the S-14 group the lipase concentration remained consistently low throughout the observation period (*Fig. 2b*).

Pancreatic enzyme concentration and output in drain fluid

The number of evaluable patients in each group was 35 until day 4, 28 on day 7, 20 on day 10 and 12 on day 12. In both

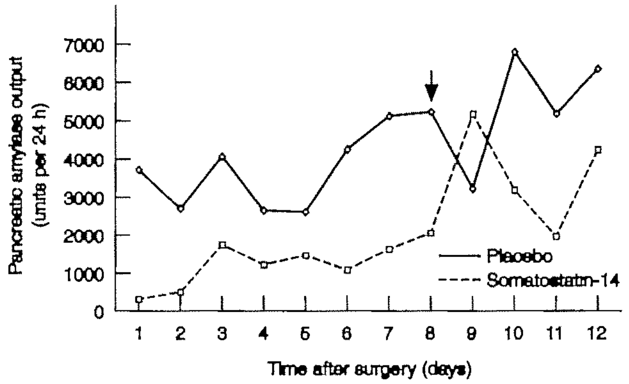


a Median output

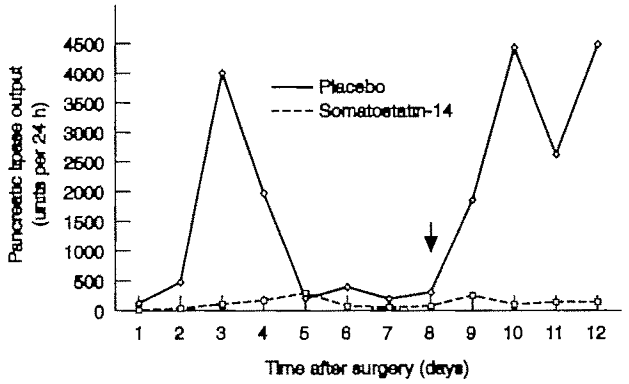


b Mean output

Fig. 1 Daily pancreatic juice output after pancreaticoduodenectomy in patients treated with somatostatin-14 or placebo; **a** median values; **b** mean values with confidence intervals. The arrow indicates when the infusion stopped



a Amylase



b Lipase

Fig. 2 Daily amylase (**a**) and lipase (**b**) output (median values) in the pancreatic juice after pancreaticoduodenectomy in patients treated with somatostatin-14 or placebo. The arrow indicates when the infusion stopped

groups, amylase and lipase concentrations were high on day 1 and decreased significantly within 4 days of surgery ($P < 0\cdot01$ and $P = 0\cdot02$ respectively) (*Fig. 3*). S-14 infusion resulted in a significantly lower amylase concentration and output in the drain fluid compared with placebo (both $P < 0\cdot05$) (*Fig. 3a*). The same trend was observed for lipase concentration and output, although significance was not achieved ($P = 0\cdot26$ and $P = 0\cdot19$ respectively) (*Fig. 3b*).

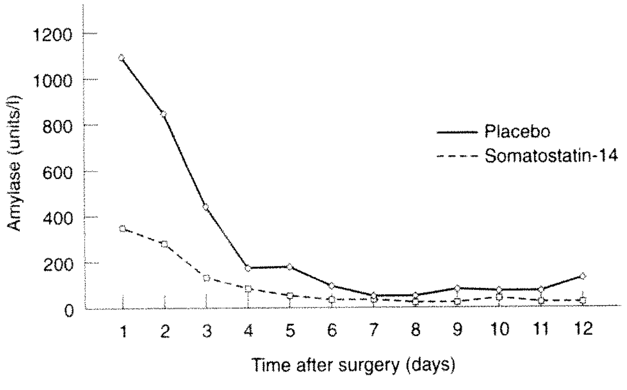
Postoperative complications

The incidence of both clinical pancreatic fistula (two of 38 *versus* eight of 37; $P < 0\cdot05$) and total pancreatic stump-related complications (five of 38 *versus* 12 of 37; $P < 0\cdot05$) was significantly lower, and the duration of hospital stay significantly shorter (18 *versus* 26 days; $P = 0\cdot01$), in the S-14 group compared with control patients (*Table 2*).

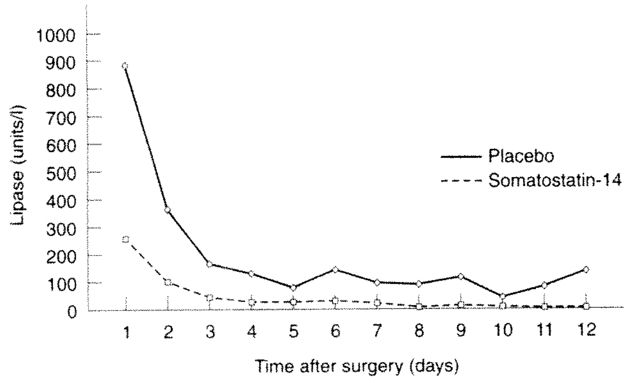
The number of other complications, the number of patients requiring further surgery and the number of postoperative deaths were similar in the two groups (*Table 2*). The overall complication rate was lower in the S-14 group, although not significantly (eight of 38 *versus* 13 of 37; $P = 0\cdot17$). Changes in serum amylase and lipase concentrations were similar in both groups.

Discussion

The fluid collected each day from the pancreatic tube, in evaluable patients, can be considered an accurate estimation of pancreatic exocrine secretion. Analysis failed to demonstrate a significant decrease in pancreatic juice and enzyme production, and therefore pancreatic exocrine secretion, following S-14 infusion. Despite recruitment of a homogeneous, high-risk patient population, likely to be



a Amylase



b Lipase

Fig. 3 Daily amylase (**a**) and lipase (**b**) concentrations (median values) in peripancreatic drain fluid after pancreaticoduodenectomy in patients treated with somatostatin-14 or placebo

Table 2 Complications and length of postoperative hospital stay

	Somatostatin (n = 38)	Placebo (n = 37)	P
Pancreatic fistula			
Clinical	2†	8†	< 0·05
Biochemical	2	2	
Infected intra-abdominal fluid collection	2‡	4§	0·37
Acute pancreatitis	1	0	0·32
Total pancreatic stump-related complications	5	12	< 0·05
Other complications	3¶	1**	0·37
Overall complications	8	13	0·17
Further surgery	4	1	0·36
Death within 30 days of surgery	2	1	0·61
Hospital stay (days)*	18(1)	26(2)	0·01

*Values are mean(s.e.m.). †One patient required further surgery; ‡two patients required further surgery and one died; §one death; ¶one cardiac-related death, two early postoperative bleeds (one required further surgery); **further surgery required because of lost biliary endoprothesis

responsive to S-14, significant interpatient variability was observed. This previously observed[4] highly skewed distribution may explain why no significant difference was detected using repeated-measures ANOVA. Analysis of median values did, however, suggest a decrease in pancreatic juice and amylase production during the 7-day S-14 infusion compared with controls.

This study assessed only basal exocrine pancreatic secretion, which is known to be reduced to a lesser extent by S-14 than stimulated secretion[7,20]. In a series of six patients receiving a regular diet, four with a pancreatic fistula and two with a pancreatic drain following pancreatic resection, octreotide reduced mean pancreatic juice output by 75 per cent and amylase production by 63 per cent[20]. In the present study, as in others[4,20], analysis of pancreatic lipase output produced inconclusive results, probably owing to substantial variation in lipase concentrations in the placebo group. In a study on a single patient with a catheter left in the pancreatic duct after operation, octreotide reduced pancreatic secretory volume and protein output compared with baseline levels[21]. In eight patients with external transduodenal drainage of the main pancreatic duct after biliary surgery, the inhibitory effect of S-14 on protein output was significantly greater than that on either water or bicarbonate production[22]. Bicarbonate concentration was not measured in the present trial.

In this study S-14 infusion resulted in a decrease in amylase concentration and output in the peripancreatic drainage fluid. Persistence of a difference between the two groups after stopping the treatment may be related to the higher fistula rate in the placebo group. It is usually speculated that the high complication rate following pancreatectomy is due to small leaks of pancreatic juice from the anastomosis and/or the pancreatic remnant itself, during the early postoperative phase[5,23]. The present data support this theory and strongly suggest that S-14 infusion decreases leakage of pancreatic enzymes from the pancreatic remnant.

S-14 administration apparently resulted in a decrease in clinical pancreatic fistula and total pancreatic stump-related complications, as well as a shorter stay in hospital. However, previous studies have not supported this unequivocally. A significant reduction in pancreatic fistula rate was reported in only three of the eight trials that assessed octreotide in pancreatic surgery[10,11,13]. Furthermore, specific analysis of high-risk patients demonstrated a significant decrease in the rate of pancreatic fistula in only two of the seven available trials[10,13]. Among the four studies that assessed octreotide in high-risk patients undergoing pancreaticoduodenectomy[12–15] only one demonstrated a significant reduction in the rate of pancreatic fistula[13]. In contrast, the four European multicentre trials observed a significant reduction in the overall incidence of complications[8–11]. The findings of the latter studies are surprising since somatostatin is designed to reduce pancreatic exocrine secretion. The mechanism by which somatostatin influences the rate of complications unrelated to the pancreas remains unclear.

Differences in study design may account for the widely differing trial outcomes. In the four European multicentre trials[8–11], all drain effluents of greater than 10 ml per 24 h of amylase-rich fluid were considered to indicate a pancreatic fistula, without examination of their clinical relevance. However, as in the American studies[14,15], the present study focused on clinical pancreatic fistulas and did not consider clinically irrelevant biochemical fistulas. Severe fibrosis is observed in over one-third of patients undergoing surgery for pancreatic carcinoma[5]. This trial aimed to enrol only genuine, high-risk patients; 85 per cent of patients recruited had a normal pancreatic remnant and only one, in the placebo group, had severe chronic pancreatitis at the transection site. In contrast to the present study, in the non-placebo-controlled study of Lowy *et al.*[14] 42 per cent of patients had undergone preoperative radiation therapy and none developed a clinical pancreatic fistula. Radiation therapy is known to decrease pancreatic exocrine function and preoperative radiation therapy has been reported to prevent pancreatic fistula formation after pancreaticoduodenectomy[24]. In the trial by Yeo *et al.*[15] pancreatic leaks were almost always observed in patients with a soft pancreatic consistency. However, even in this high-risk group, octreotide demonstrated no benefit. In the two American, single-institution studies[14,15] highly experienced pancreatic surgeons performed the surgery and the incidence of pancreatic fistula was very low, perhaps too low to be affected by somatostatin. Temporary stenting and external drainage of the pancreatic duct resulted in reduced leakage following pancreaticojejunostomy[25]. However, in the present study stented anastomosis was associated with a significantly lower fistula rate in patients who received S-14 infusion (two of 38) than in the placebo group (eight of 37).

All previous trials have assessed octreotide, a synthetic, long-acting somatostatin analogue administered by subcutaneous injection. There are data suggesting that octreotide treatment may be associated with clinically relevant changes in serum concentration, leading to a loss of enzyme-inhibitory activity[21–24,26]. Because of its short half-life, S-14 requires continuous intravenous infusion, which may result in a more consistently maintained serum concentration. In addition, octreotide does not bind to all of the identified somatostatin receptor (SSTR) subtypes, including SSTR-1 (located in the gastrointestinal tract) and SSTR-4 (located in the pancreatic islets)[27,28]. Therefore, the spectrum of therapeutic efficacy of octreotide may differ from that of somatostatin. Administration of octreotide is recommended before operation. However, because pancreatic juice output is very low in the first few hours after operation and S-14 infusion is effective immediately, in this study drug administration was started the day after surgery. The present study, however, demonstrated a high enzyme concentration in both the pancreatic juice and peripancreatic drainage fluid; in light of this, S-14 administration at the time of surgery is recommended in future.

This study strongly suggested that in high-risk patients undergoing pancreaticoduodenectomy for malignancy, S-14 infusion resulted in decreased postoperative pancreatic juice leakage from the pancreatic remnant. However, the effect of S-14 on pancreatic exocrine secretion itself remains difficult to demonstrate. Further larger trials, incorporating cost-effectiveness analyses, would be useful.

Acknowledgements

The following surgical centres participated in this study: Department of Surgery, Hotel Dieu, Lyon (C. Gouillat, P. Berard, P. Y. Chavatte, D. Manganas); Department of Surgery and Transplantation, Hôpital Edouard Herriot, Lyon (C. Partensky, V. Frering, S. Barcet); Department of Surgery and Transplantation, Hôpital de la Croix Rousse, Lyon (J. Baulieux, C. Ducerf, E. de la Roche, M. Adham); Department of Surgery, Hotel Dieu, Clermont-Ferrand (J. Chipponi, D. Pezet, K. Slim, Y. Riff, J. F. Richard); Department of Surgery, Hôpital St Andre, Bordeaux (J. Saric, J. Carles, E. Rullier); Department of Gastroenterology and Gastrointestinal Surgery, Institut Mutualiste Montsouris, Paris (B. Gayet, T. Perniceni, M. Boudet, P. Levy, F. Mal); Department of Surgery, Hôpital Bellevue, St Etienne (J. G. Balique, J. Porcheron, A. Zattara); and Department of Surgery, University Hospital Grenoble (C. Letoublon, C. Arvieux, J. L. Faucheron). This study was supported by a grant from UCB Pharma SA, Nanterre, France.

References

1 Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al.* Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226:** 248–60.
2 Bartoli FG, Arnone GB, Ravera G, Bachi V. Pancreatic fistula and relative mortality in malignant disease after pancreatoduodenectomy. Review and statistical meta-analysis

regarding 15 years of literature. *Anticancer Res* 1991; **11:** 1831–48.

3 Rosenberg L, MacNeil P, Turcotte L. Economic evaluation of the use of octreotide for prevention of complications following pancreatic resection. *J Gastrointest Surg* 1999; **3:** 225–32.

4 Hamanaka Y, Nishihara K, Hamasaki T, Kawabata A, Yamamoto S, Tsurumi M *et al.* Pancreatic juice output after pancreaticoduodenectomy in relation to pancreatic consistency, duct size, and leakage. *Surgery* 1996; **119:** 281–7.

5 Al Sharaf K, Ihse I, Dawiskiba S, Andrén-Sandberg A. Characteristics of the gland remnant predict complications after subtotal pancreatectomy. *Dig Surg* 1997; **14:** 101–6.

6 Berberat PO, Friess H, Uhl W, Büchler MW. The role of octreotide in the prevention of complications following pancreatic resection. *Digestion* 1999; **60**(Suppl 2): 15–22.

7 Beglinger C, Drewe J. Somatostatin and octreotide: physiological background and pharmacological application. *Digestion* 1999; **60**(Suppl 2): 2–8.

8 Büchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H *et al.* Role of octreotide in the prevention of postoperative complications following pancreatic resection. *Am J Surg* 1992; **163:** 125–31.

9 Pederzoli P, Bassi C, Falconi M, Camboni MG. Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. Italian Study Group. *Br J Surg* 1994; **81:** 265–9.

10 Montorsi M, Zago M, Mosca F, Capussotti L, Zotti E, Ribotta G *et al.* Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial. *Surgery* 1995; **117:** 26–31.

11 Friess H, Beger HG, Sulkowski U, Becker H, Hofbauer B, Dennler HJ *et al.* Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis. *Br J Surg* 1995; **82:** 1270–3.

12 Habib E, Elhadad A, Fourtanier G, Chipponi J, Fagniez PL, Hay JM *et al.* Place de l'octréotide dans la prévention des complications chirurgicales après pancréatectomie. Etude contrôlée multicentrique. *Ann Chir* 1998; **52:** 671–2(Abstract).

13 Briceno Delgado FJ, Lopez Cillero P, Rufian Pena S, Solorzano Peck G, Mino Fugarolas G, Pera Madrazo C. A prospective-randomized study on the usefulness of octreotide in the prevention of complications after cephalic duodeno-pancreatectomy. *Rev Esp Enferm Dig* 1998; **90:** 687–4.

14 Lowy AM, Lee JE, Pisters PWT, Davidson BS, Fenoglio CJ, Stanford P *et al.* Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. *Ann Surg* 1997; **226:** 632–41.

15 Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA *et al.* Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000; **232:** 419–29.

16 Klempa I, Schwedes U, Usadel KH. Verhütung von postoperativen pankreatitishen komplikationen nach duodenopankreatektomie durch Somatostatin. *Chirurg* 1979; **50:** 427–31.

17 Beguiristain A, Espi A, Balen E, Pardo F, Hernandez Lizoain JL, Alvarez Cienfuegos J. Profilaxis con somatostatina tras duodenopancreatectomia cefalica. *Rev Esp Enferm Dig* 1995; **87:** 221–4.

18 Van Hee R, De Laet I, Salgado R, Ysebaert D. The influence of somatostatin on postoperative outcome after elective pancreatic surgery. *Acta Chir Belg* 1998; **98:** 62–5.

19 Hamanaka Y, Suzuki T. Total pancreatic duct drainage for leakproof pancreatojejunostomy. *Surgery* 1994; **115:** 22–6.

20 Williams ST, Woltering EA, O'Dorisio TM, Fletcher WS. Effect of octreotide acetate on pancreatic exocrine function. *Am J Surg* 1989; **157:** 459–62.

21 Jenkins SA, Nott DM, Baxter JN. Fluctuations in the secretion of pancreatic enzymes between consecutive doses of octreotide: implications for the management of fistulae. *Eur J Gastroenterol Hepatol* 1995; **7:** 255–8.

22 Gullo L, Priori P, Scarpignato C, Baldoni F, Mattioli G, Barbara L. Effect of somatostatin 14 on pure human pancreatic secretion. *Dig Dis Sci* 1987; **32:** 1065–70.

23 Burdy G, Attal E, Frileux P, Dalban-Sillas B, Safar MH, Voinchet O *et al.* Analyse du liquide de drainage après duodénopancréatectomie céphalique: un critère de surveillance fiable. *Ann Chir* 1999; **53:** 191–200.

24 Ishikawa O, Ohigashi H, Imaoka S, Teshima T, Inoue T, Sasaki Y *et al.* Concomitant benefit of preoperative irradiation in preventing pancreas fistula formation after pancreatoduodenectomy. *Arch Surg* 1991; **126:** 885–9.

25 Roder JD, Stein HJ, Bottcher KA, Busch R, Heidecke CD, Siewert JR. Stented *versus* nonstented pancreaticojejunostomy after pancreatoduodenectomy: a prospective study. *Ann Surg* 1999; **229:** 41–8.

26 Friess H, Bordihn K, Ebert M, Malfertheiner P, Kemmer T, Dennler HJ *et al.* Inhibition of pancreatic secretion under long-term octreotide treatment in humans. *Digestion* 1994; **55**(Suppl 1): 10–15.

27 Patel YC, Srikant CB. Subtype selectivity of peptide analogs for all five cloned human somatostatin receptors (hsstr 1–5). *Endocrinology* 1994; **135:** 2814–17.

28 Scarpignato C, Pelosini I. Somatostatin for upper gastrointestinal hemorrhage and pancreatic surgery. A review of its pharmacology and safety. *Digestion* 1999; **60**(Suppl 3): 1–16.

Original article

Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma

M. Shimada, Y. Yamashita, S. Aishima*, K. Shirabe, K. Takenaka† and K. Sugimachi

Departments of Surgery and Science and *Surgical Pathology, Graduate School of Medical Sciences, Kyushu University and †Fukuoka City Hospital, Fukuoka 812-0046, Japan

Correspondence to: Dr M. Shimada, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (e-mail mshimada@surg2.med.kyushu-u.ac.jp)

Background: Hepatectomy with extensive lymph node dissection is the standard operation for intrahepatic cholangiocarcinoma (IHCC). However, lymph node dissection may not always be effective at reducing tumour recurrence.

Methods: Forty-nine patients with IHCC who underwent hepatectomy were investigated to determine patterns of tumour recurrence and to estimate the value of lymph node dissection during resection.

Results: At hepatectomy most metastatic lymph nodes were identified at least to the level of group 2 lymph nodes. Among 23 patients who developed recurrence, 17 had liver metastases and the other six had recurrence at other sites, mainly in the peritoneum. Poorly differentiated histology was related to the development of liver metastases. No patient with the intraductal growth type of IHCC had tumour recurrence. Lymph node dissection did not appear to improve patient survival. Histological findings of lymph node metastases and intrahepatic metastases were independent indicators of poor prognosis.

Conclusion: Lymph node metastases were seldom limited to the regional lymph nodes; most tumour recurrence occurred in the liver. Lymph node dissection did not appear to improve patient survival. Lymph node dissection alone is not likely to improve the prognosis without further control of liver metastases.

Paper accepted 27 May 2001

British Journal of Surgery 2001, 88, 1463–1466

Introduction

Intrahepatic cholangiocarcinoma (IHCC) is a rare primary liver cancer and has a poor prognosis. The following factors have been reported to affect the prognosis: macroscopic classification[1], lymph node metastases[2–4], vascular invasion[5] and a positive surgical margin[6]. The authors have also reported that either expression of matrix metalloproteinase 9[7] or abundant stroma in the tumour (scirrhous type)[8] are poor prognostic indicators for IHCC. Furthermore, a sarcomatous variant of IHCC is more malignant than standard IHCC[9].

Regarding the treatment strategy, extensive hepatectomy with extended lymph node dissection produced a better outcome[10]. In hilar cholangiocarcinoma either extended resection or liver transplantation, together with pancreaticoduodenectomy, has been suggested as a potentially curative resection which provides a favourable prognosis[11,12]. However, such extensive surgery has significant potential postoperative morbidity and mortality[5,13].

No clear guidelines on lymph node dissection exist. Furthermore, there are no detailed reports of recurrence patterns after treatment. Certain categories of IHCC have a more favourable prognosis and treatment could be less extensive[14,15].

The present report describes an experience of treating IHCC. Factors that influenced recurrence patterns and the role of extensive lymph node dissection were clarified.

Patients and methods

Forty-nine patients who underwent hepatic resection for IHCC at Kyushu University Hospital between August 1985 and December 1999 were included in this study. The mean follow-up was 29 months and included monthly measurement of carcinoembryonic antigen and carbohydrate 19-9 (CA19-9) levels, and computed tomography and ultrasonography every 3 months.

Macroscopic and microscopic types were defined, and regional lymph nodes were grouped according to the

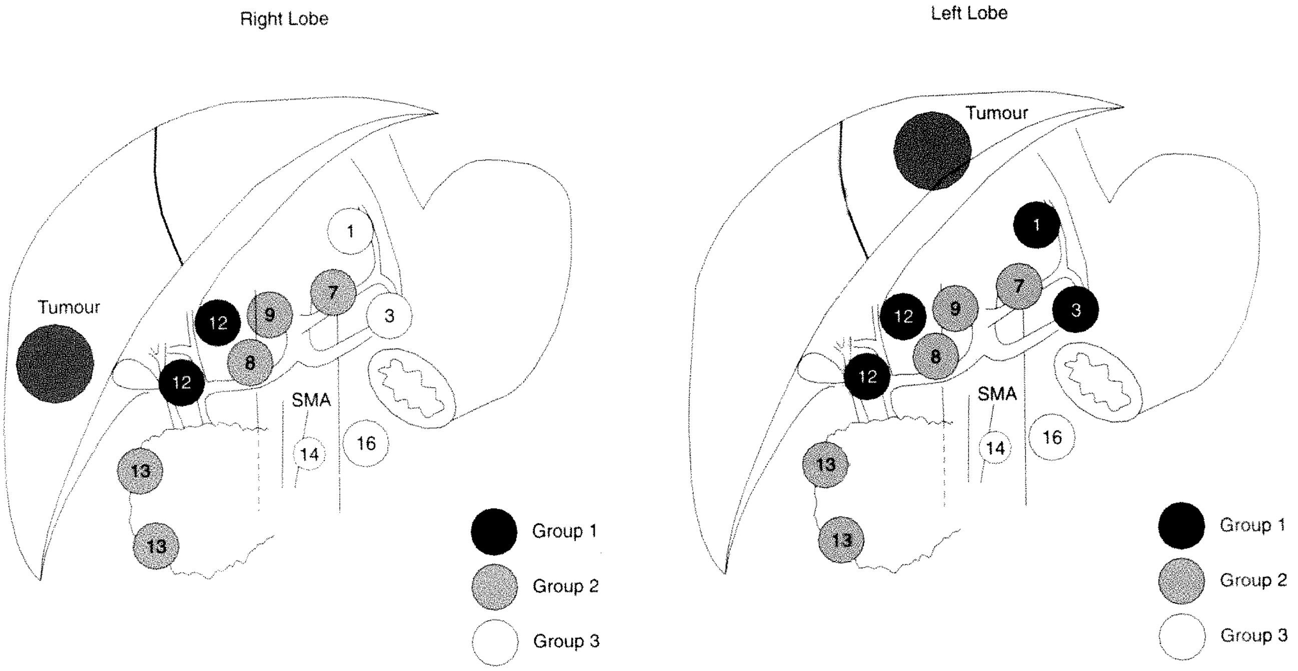


Fig. 1 Grouping of regional lymph nodes according to the Classification of Primary Liver Cancer by the Liver Cancer Study Group of Japan[16]. 1, Lymph nodes in the right cardial region; 3, lymph nodes along the lesser curvature of the stomach; 7, lymph nodes along the left gastric artery; 8, lymph nodes along the common hepatic artery; 9, lymph nodes along the coeliac artery; 12, lymph nodes in the hepatoduodenal ligament; 13, lymph nodes on the posterior surface of the pancreas head; 14, lymph nodes at the root of mesentery; 16, lymph nodes around the abdominal aorta. Group 3 lymph nodes are distant nodes beyond group 2 nodes. SMA, superior mesenteric artery

Classification of Primary Liver Cancer by the Liver Cancer Study Group of Japan[16]. The right and left lobes of the liver have different routes of lymphatic drainage according to the tumour location (*Fig. 1*) so the grouping of regional lymph nodes is distinguished by the tumour location. With respect to macroscopic typing, IHCC was classified into the following types: mass-forming type (characterized by the presence of a round-shaped mass in the liver parenchyma, with a distinct border), periductal infiltrating type (characterized by tumour infiltration along the bile duct and occasionally involving the surrounding blood vessels or hepatic parenchyma) or intraductal growth type (characterized by papillary or granular growth, or both, within the bile duct lumen, occasionally involving superficial extension).

Tumour recurrence patterns were investigated by studying 23 of 30 patients who developed recurrence; detailed information was available about tumour recurrence in these patients. Seventeen of the 23 patients had liver metastases and six had other sites of metastatic disease. Clinicopathological variables related to the development of liver metastases were investigated.

The survival of patients who had lymph node dissection during resection (n = 41) was compared with that of those without lymph node dissection (n = 8). Regarding the level of dissection in the 41 patients who had lymphadenectomy, group 1 lymph nodes alone were removed in six patients, group 2 lymph nodes in 18 patients and group 3 lymph nodes in 17 patients (*Fig. 1*). In most patients lymph node dissection was performed at least to the level of group 2 lymph nodes; however, in poor-risk patients, and those early in the series, only group 1 lymph nodes were removed. The extent of lymph node dissection was similar for right- and left-sided tumours, except for dissection of lymph nodes along the lesser curvature of the stomach for tumours located in the left lobe of the liver (*Fig. 1*).

Patient survival was calculated by the product limit method of Kaplan and Meier[17], and differences in survival between the groups were compared using the log rank test[18]. To investigate prognostic factors in all patients, using each clinicopathological variable including continuous ones, the independent prognostic factors were selected in multivariate analysis using Cox's proportional hazards model[19]. The continuous variables were classified into two groups, according to the median value of each variable.

Results

The postoperative morbidity rate was ten of 49, and there were two postoperative deaths in hospital. However, there were no in-hospital deaths in the 40 most recent resections since September 1991. The overall patient survival rates were 61 per cent at 1 year, 36 per cent at 3 years and 28 per cent at 5 years (*Fig. 2*).

Among 41 patients who underwent extended lymph node dissection, 24 had metastatic lymph nodes identified on histology. Only three of 24 patients had lymph node metastases in only group 1 nodes; the other 21 all had involvement of group 2 or 3 lymph nodes.

Two patients had the intraductal growth type of IHCC; neither developed recurrent disease. Among the 23 patients who developed recurrence, 17 patients had liver metastases and the other six had metastases in other organs, mainly the peritoneum. Six of the 17 patients with liver metastases had simultaneous recurrence at other sites. Most liver metastases occurred in the remnant liver after major hepatectomy; a few developed in the contralateral lobe after minor hepatectomy.

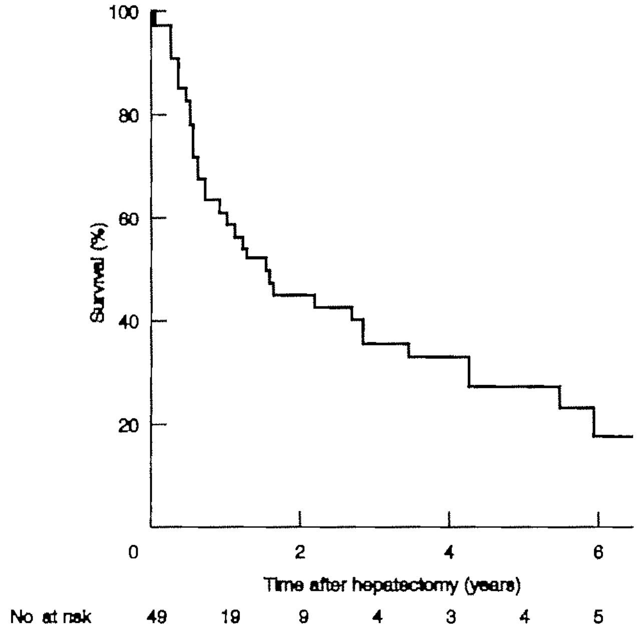


Fig. 2 Overall survival in 49 patients who had surgical resection of intrahepatic cholangiocarcinoma.Survival rates were 61 per cent at 1 year, 36 per cent at 3 years and 28 per cent at 5 years

There was no difference in survival rate between patients who had lymph node dissection and those who did not. Patients who had extended lymph node dissection were more likely to have had a major hepatectomy (33 of 41 *versus* four of eight) and a longer operation (mean(s.d.) 524(182) *versus* 284(69) min). Both in-hospital deaths occurred in patients who had extended lymph node dissection.

The CA19-9 level was lower in patients who had recurrent disease in the liver than in patients with recurrence who had metastases outwith the liver (median 22 *versus* 7730 units/ml). Patients who had liver metastases were more likely to have poorly differentiated histology (nine of 17) than patients with other metastases (none of six). The rate of lymph node metastases detected histologically in patients with liver metastases (seven of 17) was lower than that in patients who had other types of metastases (six of six).

Lymph node metastases identified on histology (relative risk (RR) 10·6) and intrahepatic metastases (RR 3·7) were both independent poor prognostic indicators.

Discussion

In this study recurrence patterns after treatment for IHCC were investigated in detail. Important findings were that lymph node metastases spread rapidly to distant nodes (group 2 or 3 lymph nodes)[20], most tumour recurrence occurred in the remnant liver, and no recurrence occurred in the intraductal growth type of IHCC.

One patient, who had IHCC in the left liver lobe, had lymph node metastases around the right cardial region, a finding similar to that of Nozaki *et al.*[21]. Such observations are reflected in the definition of regional lymph nodes in the Classification of Primary Liver Cancer by the Liver Cancer Study Group of Japan[16]. As soon as lymph node metastases occur, positive nodes are rarely limited to the regional (group 1) lymph nodes. Therefore, if lymph node dissection is to be effective, extended lymph node dissection is required, including group 2 or 3 (distant) lymph nodes. The present study suggested that extended lymph node dissection did not prolong survival. Furthermore, most recurrence involved liver metastases; lymph node dissection was unlikely to improve the prognosis without control of liver metastases.

In the present study, two patients died after lymph node dissection. Although the number of patients studied was small, this may illustrate the potential operative risk of extended liver resection including lymph node dissection. Other studies have reported similar findings[5,13].

This study showed that the histological findings of positive lymph node metastases and positive intrahepatic metastases were independent poor prognostic factors. No patient with these survived longer than 3 years. Long-term survivors who had distant lymph node metastases at operation have occasionally been reported[22]. Extended lymph node dissection for IHCC does not seem to offer any advantage.

Using the macroscopic classification, only the intraductal growth type of IHCC did not recur in this study. Suh *et al.*[14] suggested that intraductal growth type IHCC should be classified separately. Periductal infiltrating IHCC has been reported to have a better prognosis than mass-forming IHCC[15], but Yamamoto *et al.*[13] stated the opposite, that periductal infiltrating IHCC has the worst prognosis. In the present study there was no difference in outcome between these two types. Therefore only the intraductal growth type of IHCC should be classified separately.

References

1 Yamamoto M, Takasaki K, Yoshikawa T, Ueno K, Nakano M. Does gross appearance indicate prognosis in intrahepatic cholangiocarcinoma? *J Surg Oncol* 1998; **69:** 162–7.

2 Casavilla FA, Marsh JW, Iwatsuki S, Todo S, Lee RG, Madariaga JR *et al.* Hepatic resection and transplantation for peripheral cholangiocarcinoma. *J Am Coll Surg* 1997; **185:** 429–36.

3 Chou FF, Sheen-Chen SM, Chen YS, Chen MC, Chen CL. Surgical treatment of cholangiocarcinoma. *Hepatogastroenterology* 1997; **44:** 760–5.

4 Chu KM, Lai EC, Al-Hadeedi S, Arcilla CE, Lo CM, Liu CL *et al.* Intrahepatic cholangiocarcinoma. *World J Surg* 1997; **21:** 301–5.

5 El Rassi ZE, Partensky C, Scoazec JY, Henry L, Lombard-Bohas C, Maddern G. Peripheral cholangiocarcinoma: presentation, diagnosis, pathology and management. *Eur J Surg Oncol* 1999; **25:** 375–80.

6 Valverde A, Bonhomme N, Farges O, Sauvanet A, Flejou JF, Belghiti J. Resection of intrahepatic cholangiocarcinoma: a Western experience. *J Hepatobiliary Pancreat Surg* 1999; **6:** 122–7.

7 Shirabe K, Shimada M, Kajiyama K, Hasegawa H, Gion T, Ikeda Y *et al.* Expression of matrix metalloproteinase-9 in surgically resected intrahepatic cholangiocarcinoma. *Surgery* 1999; **126:** 842–6.

8 Kajiyama K, Maeda T, Takenaka K, Sugimachi K, Tsuneyoshi M. The significance of stromal desmoplasia in intrahepatic cholangiocarcinoma: a special reference of 'scirrhous-type' and 'nonscirrhous-type' growth. *Am J Surg Pathol* 1999; **23:** 892–902.

9 Shimada M, Takenaka K, Rikimaru T, Hamatsu T, Yamashita Y, Kajiyama K *et al.* Characteristics of sarcomatous cholangiocarcinoma of the liver. *Hepatogastroenterology* 2000; **47:** 956–61.

10 Isaji S, Kawarada Y, Taoka H, Tabata M, Suzuki H, Yokoi H. Clinicopathological features and outcome of hepatic resection for intrahepatic cholangiocarcinoma in Japan. *J Hepatobiliary Pancreat Surg* 1999; **6:** 108–16.

11 Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N *et al.* Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999; **230:** 808–18.

12 Kosuge T, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg* 1999; **230:** 663–71.

13 Yamamoto M, Takasaki K, Yoshikawa T. Extended resection for intrahepatic cholangiocarcinoma in Japan. *J Hepatobiliary Pancreat Surg* 1999; **6:** 117–21.

14 Suh KS, Roh HR, Koh YT, Lee KU, Park YH, Kim SW. Clinicopathologic features of the intraductal growth type of peripheral cholangiocarcinoma. *Hepatology* 2000; **31:** 12–17.

15 Higashi M, Yonezawa S, Ho JJ, Tanaka S, Irimura T, Kim YS *et al.* Expression of MUC1 and MUC2 mucin antigens in intrahepatic bile duct tumors: its relationship with a new morphological classification of cholangiocarcinoma. *Hepatology* 1999; **30:** 1347–55.

16 Liver Cancer Study Group of Japan. *Classification of Primary Liver Cancer.* 1st English ed. Tokyo: Kanehara, 1997.

17 Kaplan GL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

18 Peto R, Pike MC. Conservation of the approximation $\Sigma(O - E)^2/E$ in the logrank test for survival data on tumor incidence data. *Biometrics* 1973; **29:** 579–84.

19 Cox DR. Regression models and life tables. *J R Stat Soc Series B* 1972; **34:** 187–220.

20 UICC International Union Against Cancer Liver (ICD-O155). In: Hermanek P, Sobin LH, eds. *TNM Classification of Malignant Tumours.* 4th ed. Berlin: Springer, 1982: 53–5.

21 Nozaki Y, Yamamoto M, Ikai I, Yamamoto Y, Ozaki N, Fujii H *et al.* Reconsideration of the lymph node metastases pattern (N factor) from intrahepatic cholangiocarcinoma using the International Union Against Cancer TNM staging system for primary liver carcinoma. *Cancer* 1998; **83:** 1923–9.

22 Murakami Y, Yokoyama T, Takesue Y, Hiyama E, Yokoyama Y, Kanehiro T *et al.* Long-term survival of peripheral intrahepatic cholangiocarcinoma with metastases to the para-aortic lymph nodes. *Surgery* 2000; **127:** 105–6.

Original article

Readmissions after pancreatoduodenectomy

R. C. I. van Geenen, T. M. van Gulik, O. R. C. Busch, L. T. de Wit, H. Obertop and D. J. Gouma

Department of Surgery, Academic Medical Center, Meibergdreef 9, PO Box 22660, 1100 DD Amsterdam, The Netherlands
Correspondence to: Professor D. J. Gouma (e-mail: d.j.gouma@amc.uva.nl)

Background: Readmission after pancreatoduodenectomy because of tumour recurrence or surgery-related complications can adversely affect patient outcome.

Methods: From October 1992 to June 1999, 283 consecutive resections were performed (243 for malignant disease and 40 for benign disease). The hospital mortality rate was 1 per cent (three of 283). All readmissions were analysed with regard to indication, treatment and outcome.

Results: One hundred and six patients (38 per cent) were readmitted, 64 (60 per cent) because of tumour recurrence and indications such as gastrointestinal obstruction ($n = 19$), biliary obstruction ($n = 15$) and pain ($n = 21$), of whom 30 patients (47 per cent) were in a preterminal condition. Median hospital stay and hospital-free survival after discharge were 14 and 51 days respectively. Median survival after surgical treatment ($n = 14$) was 58 days, and ascites was significantly associated with poor survival. Forty-seven (44 per cent) of the patients were readmitted for surgical complications such as abscess ($n = 11$), fistula ($n = 8$) and gastrointestinal obstruction ($n = 8$). Median hospital stay was 15 days and median hospital-free survival after discharge was 1035 days.

Conclusion: Readmission after pancreatoduodenectomy was common (38 per cent), 60 per cent for tumour recurrence and 44 per cent for surgery-related complications. Survival after surgical bypass procedures for tumour recurrence was limited, particularly when ascites was present. Patients readmitted for complications of surgery had a good prognosis.

Paper accepted 20 June 2001

British Journal of Surgery 2001, 88, 1467–1471

Introduction

Postoperative morbidity and mortality rates after (pylorus preserving) pancreatoduodenectomy performed for periampullary tumours, including pancreatic malignancies, have decreased to acceptable levels[1–6]. This has encouraged surgeons to perform the procedure even in patients with a small chance of complete resection or as a palliative operation[7]. The 5-year survival rate after pancreatoduodenectomy for malignant disease has been reported between 1 and 25 per cent for pancreatic adenocarcinoma[5,8,9], and between 6 and 50 per cent for ampullary carcinoma[8,10–12]. The majority of these patients develop tumour recurrence during follow-up, indicating that the treatment in these patients has been palliative. The quality of long-term outcome for these patients should be taken into account if resection as a form of palliation is to be acceptable. Readmission rate is an easily measured and objective variable associated with the quality of long-term outcome, reflecting the sequelae of tumour recurrence and late complications related to the initial surgical procedure.

Knowledge of the incidence and management of patients readmitted after pancreatoduodenectomy may contribute positively to an improvement in quality of care of these patients. The aim of this study was to analyse readmissions after resection with regard to indication, treatment and outcome thereafter.

Patients and methods

Between October 1992 and June 1999, 283 consecutive patients underwent pancreatoduodenectomy, 243 for malignant disease and 40 for benign disease. The hospital mortality rate was 1 per cent (three of 283), the morbidity rate was 48 per cent (135 of 283) and the median hospital stay was 16 (range 6–222) days, as reported previously[13].

Data on the resection were collected from a prospective database that included variables recorded at the initial hospitalization and during follow-up. Follow-up data were completed from the outpatient files, the general practitioners and physicians outside the Academic Medical Center (AMC). Data on readmissions were obtained from the patient records and via involved physicians outside the AMC in the case of patients readmitted elsewhere. Only four of the 280 surviving patients were lost to follow-up.

Readmissions were divided in two categories, those required for tumour recurrence and those for complications of the initial surgical procedure. Patients could be readmitted for sequelae of tumour recurrence and/or for complications of the initial surgical procedure in separate readmissions, and thus the number of readmissions could be higher than the number of patients readmitted. A sequela of tumour recurrence was defined as locoregional tumour recurrence (or progression after resection with tumour-positive margins) or distant metastases, assessed by radiology or proven histologically up to an arbitrary period of 3 months after readmission. Patients with readmissions resulting in death during or within 1 month after readmission were defined as being in a preterminal condition. Readmissions for complications of the initial surgical procedure were defined as readmission as a result of complications of the procedure in the absence of tumour recurrence during the 3 months after operation. Future follow-up may of course still further increase the number of patients with tumour recurrence and surgery-related readmissions.

Readmissions were analysed with regard to indication, diagnosis, treatment, hospital stay, interval between the resection and readmission, and hospital-free survival thereafter. Prognostic factors for survival after surgical treatment for tumour recurrence were analysed with log rank tests. $P < 0.05$ was considered statistically significant.

Results

Of the 280 patients who were followed up for a median of 17 (range 1–91) months, 106 patients (53 men and 53 women) with a median age of 64 (range 37–80) years were readmitted. Of these patients, 64 (60 per cent) of 106 were readmitted for sequelae of tumour recurrence and 47 (44 per cent) for complications of the initial surgical procedure. Five (5 per cent) of the patients underwent separate readmissions for sequelae of tumour recurrence and for complications of the initial surgical procedure. Nineteen patients underwent multiple readmissions. The total number of readmissions was 146.

Readmissions for sequelae of tumour recurrence

Of the 240 patients with malignant disease 64 patients (27 per cent) were readmitted after resection for sequelae of tumour recurrence. The initial surgical procedure was a pylorus-preserving pancreatoduodenectomy in 53 patients and a classical Whipple's procedure in 11. The tumour was located in the pancreatic head ($n = 41$), the distal common bile duct ($n = 9$) or the ampulla ($n = 14$). Microscopic tumour-free resection margins had been obtained in 39 (61 per cent) of the 64 patients. In 25 (39 per cent) of the patients there was tumour progression after resection with tumour-positive resection margins.

Patients were readmitted after a median of 7 (range 1–53) months after resection. Readmissions were for preterminal care in 30 (47 per cent) of these patients. Reasons for readmission are summarized in *Table 1*.

Treatment

Gastrointestinal obstruction was treated with a surgical bypass procedure in nine, (par)enteral feeding in three and non-invasive palliation in seven patients. Biliary obstruction of the afferent loop or the hepaticoenterostomy was treated with a surgical bypass procedure in five patients, percutaneous transhepatic cholangiography (PTC) with endoprostheses in seven, PTC with external drainage in two patients, and non-invasive palliation in one terminally ill patient. Pain was treated with percutaneous chemical splanchnectomy in five, and medical treatment in 16

Table 1 Readmissions after pancreatoduodenectomy for sequelae of recurrent disease and subsequent outcome in 64 patients

Complication	No. of patients*‡	Time before readmission (months)†	In-hospital death	Hospital stay (days)†	Survival after readmission (days)†
Gastrointestinal obstruction	19 (30)	9 (1–53)	5	18 (0–49)	48 (0–537)
Biliary obstruction	15 (23)	10 (4–30)	2	15 (2–75)	74 (15–471)
Pain	21 (33)	6 (1–43)	4	9 (2–18)	74 (4–1054)
General discomfort	8 (12)	10 (2–16)	0	5 (1–36)	129 (14–129)
Ascites	4 (6)	24 (2–40)	0	10 (7–31)	37 (17–128)
Tumour bleeding	3 (5)	12 (7–17)	0	10 (2–26)	76 (26–76)
Adjuvant chemoradiation	7 (11)	3 (1–25)	0	7 (1–16)	395 (36–1728)
Palliative chemotherapy	1 (2)	8	0	1	90

*Values in parentheses are percentages; †values are median (range). ‡Patients were scored for one or more different readmissions for sequelae of recurrent disease

Table 2 Patient characteristics and outcome after surgical treatment of 14 patients with gastrointestinal and biliary obstruction due to tumour recurrence

Patient characteristics	
Clinical type of obstruction	
Biliary obstruction	5
Gastrointestinal obstruction	7
Biliary and gastrointestinal obstruction	2
Time before readmission (months)*	8 (4–21)
Surgery	
Anatomical site of obstruction	
Afferent loop	4
Gastroenterostomy	3
Afferent loop and gastroenterostomy	7
Surgical technique	
Hepaticoenterostomy	1
Enteroenterostomy	3
Gastroenterostomy	5
Enteroenterostomy and gastroenterostomy	5
Pathology	
Local tumour recurrence	2
Metastases	1
Local tumour recurrence and metastases	11
Outcome	
Hospital stay (days)*	18 (1–49)
Survival (days)*	58 (7–486)

*Values are median (range)

patients. General discomfort was treated by non-surgical means. In three patients ascites was drained percutaneously and one patient was treated for ascites with a stent in the portal vein. Two patients who suffered from tumour bleeding received blood transfusions and one patient was also treated successfully with external radiotherapy (8 Gy). In one patient laparotomy was performed in an attempt to resect the pancreatic tail for tumour recurrence but liver metastases were found. Adjuvant chemoradiation therapy necessitated readmission in seven patients who were included in a trial by the European Organisation for Research and Treatment for Cancer (EORTC)[14]. Palliative chemotherapy with gemcitabin was used in one patient.

Outcome

Median hospital stay was 14 (range 0–349) days. Median hospital-free survival after readmission of these 64 patients was 51 (range 0–1045) days and 351 (range 47–1805) days after resection. At the end of the follow-up period 83 of 240 patients with malignant disease had not been readmitted and were still alive and therefore at risk for readmission after a median follow-up of 17 (range 1–79) months.

Subanalysis of surgical treatment

Patients with a gastrointestinal or biliary obstruction and proven tumour recurrence who were treated surgically (n = 14) were analysed separately (*Table 2*). After surgical treatment median hospital stay was 18 (range 1–49) days. Median survival time after surgical treatment for disease-related readmissions was 58 (range 7–486) days. Several variables were tested for their influence on survival: original tumour location, type of obstruction, site of obstruction, presence of metastases and ascites. Median survival for patients with ascites who underwent surgery was significantly less than that in those without (41 *versus* 183 days; P = 0·01). The original tumour location, site of obstruction or presence of metastases did not influence median survival significantly. There was a trend toward a shorter survival after surgery for gastrointestinal obstruction compared with biliary obstruction (41 *versus* 254 days respectively; P = 0·09).

Readmissions for complications of the initial surgical procedure

Of the 280 patients who were followed after pancreatoduodenectomy 47 (17 per cent) were readmitted for complications of the initial surgical procedure after a median of 6 (range 1–57) months. The mortality rate after readmission for complications related to the initial surgical procedure was 4 per cent (two of 47). The median hospital stay after readmission for complications was 7 (range 1–131) days. The median hospital-free survival after discharge was 1035 (range 0–1782) days.

Thirty-five patients were readmitted after a median of 5 (range 0–57) months for complications after resection for malignant disease, without any sign of tumour progression. Most frequent complications were abscess (n = 9), gastrointestinal obstruction (n = 7) and fistula (n = 7) (*Table 3*). The median hospital-free survival time after readmission, including two patients who died, was 843 (range 0–1587) days and 926 (range 47–2726) days after resection.

Twelve patients were readmitted after a median period of 12 (range 1–29) months for complications after resection for the following benign diseases: chronic pancreatitis (n = 8), neuroendocrine tumour (n = 3) and duodenal adenoma (n = 1). The most frequent complication was incisional hernia (n = 4) (*Table 3*). After median follow-up of 29 (range 1–81) months all patients with benign disease were alive.

Discussion

Although mortality and morbidity rates after pancreatoduodenectomy have reached acceptable levels, a rather high percentage of patients (38 per cent) needs to be readmitted in the months after resection. In another study a readmission rate of only 11 per cent after pancreatoduodenectomy was reported[15]. In that study readmissions at hospitals

Table 3 Readmissions for complications of the initial surgical procedure

Complication	No. of patients†	Time before readmission (months)*	In-hospital death	Hospital stay (days)*
Total no. of patients	47	6 (0–57)	2	7 (1–131)
Malignant pathology	35	5 (0–57)	2	8 (1–131)
Abscess	9	1 (0–22)	1	14 (7–94)
Gastrointestinal obstruction	7	4 (1–6)	0	10 (1–63)
Fistula	7	9 (1–57)	1	8 (2–95)
Biliary obstruction	4	1 (1–24)	0	6 (2–9)
Anastomotic ulcer	3	7 (1–11)	0	6 (2–9)
Pancreatitis	3	7 (5–25)	0	6 (4–8)
Hypoglycaemia	2	0 and 9	0	7 and 9
Other	5	3 (0–29)	0	5 (4–9)
Benign pathology	12	12 (1–29)	0	5 (3–38)
Incisional hernia	4	25 (11–29)		5 (4–6)
Abscess/fistula	3	2 (2–2)		5 (5–27)
Anastomotic ulcer	2	7 and 23		3 and 11
Pseudocyst	2	21 and 18		1 and 5
Gastrointestinal obstruction	1	14		11
Pancreatitis	1	14		8

*Values are median (range). †Patients were scored for one or more different readmissions

in the residential area of the patients may not have been taken into account. In the present series all readmissions were also checked with the general practitioner. The discrepancy could also be due to differences in the length of follow-up. However, the median follow-up after resection (17 months) in this study exceeded the median time to readmission for malignant (7 months) or benign (6 months) disease.

In patients readmitted for sequelae of tumour recurrence the most common reasons were gastrointestinal obstruction (30 per cent), biliary obstruction (23 per cent) or pain (33 per cent). Of all patients who underwent resection for malignant disease, 8 per cent were readmitted with gastrointestinal obstruction, compared with 2–5 per cent reported in the literature[15–17]. This might be explained by different definitions of gastrointestinal obstruction. When patients with proven obstruction treated by conservative means were excluded, an incidence of gastrointestinal obstruction of 4 per cent was estimated. In the present series survival after gastrointestinal obstruction was limited. Even after surgical bypass the median survival was only 41 days. Ascites was a negative prognostic factor in these patients and one could argue for refraining from surgery. For multifocal obstruction surgical bypass is often not feasible. In the case of an isolated malignant gastric outlet obstruction endoscopic insertion of an expandable stent may also offer relief[18–20]. Apart from an anatomical obstruction, a functional obstruction caused by neural invasion by the tumour recurrence might be present in some patients.

Biliary obstruction resulting from obstruction of the afferent loop or the hepaticoenterostomy due to tumour recurrence was found in 6 per cent and is in accordance with previously reported series (2–6 per cent)[15–17]. The absence of distant metastases and the reasonable general condition of the patient allowed surgical intervention. However, survival after surgery was limited. In patients with biliary obstruction and ascites, surgical bypass should not be performed, as this is associated with poor survival.

Pain was the most frequent cause of readmission (n = 21). These findings are in accordance with the literature; pain is a frequent symptom in patients with pancreatic cancer[21] and is associated with a poor prognosis[22,23]. Despite the various methods of pain treatment that are possible in these patients, including thoracoscopic splanchnectomy, percutaneous chemical splanchnectomy and external-beam radiotherapy, most patients were treated with analgesics. These patients are in poor condition; invasive treatment or radiotherapy requires hospital visits and can thereby further decrease quality of life.

After resection 17 per cent of the patients presented with complications of the initial surgical procedure, 35 of 240 and 12 of 40 after resection for malignant and benign disease respectively. This was higher than expected. This might partly be the result of a relatively early discharge of patients so that some of these complications, for instance abscess, did not occur during the initial admission but shortly after discharge. However, the majority of these complications developed more than 2 weeks after discharge. The high percentage of readmissions for complications after resection for benign disease might also be the result of the relatively long survival time and the higher chance of developing a complication. Recurrent tumour as the underlying pathology of a complication cannot always be proven or excluded. This complicates the decision about therapy, especially in cases of gastrointestinal or biliary obstruction where invasive treatment such as bypass surgery can be helpful in treating benign obstructions.

In conclusion, the readmission rate after an intentionally curative resection for periampullary malignancy was 27 per cent. Half of these patients were readmitted in a preterminal stage. Surgical reinterventions for sequelae of tumour recurrence resulted in hospitalization for approximately one-third of the limited survival time and therefore are not recommended. Ascites is a significant predictor of poor survival and should therefore be considered a contra-indication to surgery. Occasionally patients benefit from surgery but they cannot be identified before operation. After pancreatoduodenectomy 17 per cent of the patients were readmitted for complications of the initial surgical procedure without tumour recurrence and had a good prognosis.

References

1 Tan HP, Smith J, Garberoglio CA. Pancreatic adenocarcinoma: an update. *J Am Coll Surg* 1996; **183**: 164–84.

2 Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF. Factors predictive of survival in ampullary carcinoma. *Ann Surg* 1998; **228**: 87–94.

3 Lillemoe KD. Current management of pancreatic carcinoma. *Ann Surg* 1995; **221**: 133–48.

4 Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. *Ann Surg* 1990; **211**: 447–58.

5 Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 1995; **221**: 59–66.

6 Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al.* Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248–57; discussion 257–60.

7 Lillemoe KD, Cameron JL, Yeo CJ, Sohn TA, Nakeeb A, Sauter PK *et al.* Pancreaticoduodenectomy. Does it have a role in the palliation of pancreatic cancer? *Ann Surg* 1996; **223**: 718–25.

8 Bakkevold KE, Kambestad B. Palliation of pancreatic cancer. A prospective multicentre study. *Eur J Surg Oncol* 1995; **21**: 176–82.

9 Takahashi S, Ogata Y, Tsuzuki T. Combined resection of the pancreas and portal vein for pancreatic cancer. *Br J Surg* 1994, **81**: 1190–3.

10 Allema JH, Reinders ME, van Gulik TM, Koelemay MJ, Van Leeuwen DJ, de Wit LT *et al.* Prognostic factors for survival after pancreaticoduodenectomy for patients with carcinoma of the pancreatic head region. *Cancer* 1995; **75**: 2069–76.

11 Andersen HB, Baden H, Brahe NE, Burcharth F. Pancreaticoduodenectomy for periampullary adenocarcinoma. *J Am Coll Surg* 1994; **179**: 545–52.

12 Nakai T, Koh K, Kawabe T, Son E, Yoshikawa H, Yasutomi M. Importance of microperineural invasion as a prognostic factor in ampullary carcinoma. *Br J Surg* 1997; **84**: 1399–401.

13 Gouma DJ, van Geenen RCI, van Gulik TM, de Haan RJ, de Wit LT, Busch OR *et al.* Rates of complications and death after pancreaticoduodenectomy. risk factors and the impact of hospital volume. *Ann Surg* 2000; **232**: 786–95.

14 Klinkenbijl JHG, Jeekel J, Sahmoud T, val Pel R, Couvreur ML, Veenhof CH *et al.* Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Ann Surg* 1999; **230**: 776–82.

15 Sperti C, Pasquali C, Piccoli A, Sernagiotto C, Pedrazzoli S. Radical resection for ampullary carcinoma: long-term results. *Br J Surg* 1994; **81**: 668–71.

16 Yeh TS, Jan YY, Chen MF. Roux loop obstruction after pancreaticoduodenectomy. *Br J Surg* 1997; **84**: 323–4.

17 Lillemoe KD, Cameron JL, Yeo CJ, Sohn TA, Nakeeb A, Sauter PK *et al.* Pancreaticoduodenectomy. Does it have a role in the palliation of pancreatic cancer? *Ann Surg* 1996; **223**: 718–25.

18 Jung GS, Song HY, Kang SG, Huh JD, Park SJ, Koo JY *et al.* Malignant gastroduodenal obstructions: treatment by means of a covered expandable metallic stent – initial experience. *Radiology* 2000; **216**: 758–63.

19 Espat NJ, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. *J Am Coll Surg* 1999; **188**: 649–55.

20 Venu RP, Pastika BJ, Kini M, Chua D, Christian R, Schlais J *et al.* Self-expandable metal stents for malignant gastric outlet obstruction: a modified technique. *Endoscopy* 1998; **30**: 553–8.

21 Yeo CJ. Pancreatic cancer: 1998 update. *J Am Coll Surg* 1998; **187**: 429–42.

22 Kelsen DP, Portenoy R, Thaler H, Tao Y, Brennan M. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. *Surgery* 1997; **122**: 53–9.

23 Andren-Sandberg A, Viste A, Horn A, Hoem D, Gislason H. Pain management of pancreatic cancer. *Ann Oncol* 1999; **10**(Suppl 4): 265–8.

Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms

J. S. Lindholt, E. J. Erlandsen* and E. W. Henneberg

Departments of Vascular Surgery and *Clinical Biochemistry, Viborg-Kjellerup County Hospital, Viborg, Denmark
Correspondence to: Dr J. S. Lindholt, Laerkevej 11, 8900 Randers, Denmark (e-mail: jslindholt@mail.tele.dk)

Background: The cysteine protease inhibitor cystatin C may play a role in the development and progression of abdominal aortic aneurysms (AAAs).
Methods: From a mass screening trial of men aged 65–73 years, 151 small AAAs were followed for a mean of 2·9 years. Of these patients, 142 had serum samples taken to determine the levels of cystatin C, creatinine and C-reactive protein (CRP).
Results: Serum cystatin C concentration correlated negatively with AAA size ($r = -0{\cdot}22$ (95 per cent confidence interval (c.i.) −0·59 to −0·02)) and annual expansion rate ($r = -0{\cdot}24$ (95 per cent c.i. −0·75 to −0·05)), persisting after adjustment for renal function, smoking, diastolic blood pressure, CRP, age and AAA size. Creatinine clearance and CRP did not correlate with size or expansion rate. Thirty-one AAAs had expanded to over 50 mm, when operation was recommended. The serum level of cystatin C was a significant predictor of this occurrence, with a sensitivity and specificity of 61 and 57 per cent respectively. However, initial AAA size had the optimal sensitivity and specificity (both 81 per cent) in this regard.
Conclusion: Deficiency of cystatin C was associated with increased aneurysm size and expansion rate, possibly due to lack of inhibition of cysteine proteases.

Paper accepted 1 July 2001

British Journal of Surgery 2001, **88**, 1472–1475

Introduction

Abdominal aortic aneurysm (AAA) seems to include an inflammatory process that involves extensive extracellular matrix degradation and remodelling of the aortic wall. Several metalloproteases[1,2] and serine proteases[3,4] have been reported to be involved. Recently, two elastolytic cysteine proteases, cathepsin S and K, were isolated and are overexpressed in atheroslerotic lesions compared with normal arteries[5]. Monocyte-derived macrophages and smooth muscle cells are present in the aneurysm wall and are capable of releasing cathepsins[6]. The potential elastolytic effect depends on the amount of inhibitors present. The most abundant extracellular inhibitor of the cysteine proteases is cystatin C. The high concentration discovered in biological fluids suggests that cystatin C is probably an important extracellular cysteine protease inhibitor[7].

In vitro studies have shown that alveolar macrophages from cigarette smokers and monocytes stimulated by interferon γ secrete less cystatin C than unstimulated macrophages or monocytes, suggesting the possibility of reduced cystatin C levels in inflammatory areas[8,9]. Cystatin C could thus play a role in the development and progression of AAA.

This study assessed whether the serum level of cystatin C is associated with the size and expansion rate of small AAAs.

Patients and methods

Between 1994 and 1998, personal identification numbers, names and addresses of all 12 665 65–73-year-old men in Viborg County were provided by the county's Health Department. After randomization, 6339 men were invited to attend for abdominal ultrasonography at their regional hospital. A doctor and a nurse, specially trained in ultrasonography, alternated between organizing and performing the scans. The B-mode scans were carried out with a small Phillips SDR 1550 (Phillips, Aarhus, Denmark) with a linear 4-mHz transducer and calliper light pen.

An AAA was defined as an infrarenal aortic diameter of 30 mm or more; patients with an AAA greater than 50 mm were referred for elective operation. Patients with an AAA of 30–49 mm were offered yearly follow-up examinations to check for expansion. The arithmetic interobserver variation (two standard deviations) of the measurements was 1·4 mm[10].

All patients with an AAA consulted the trial doctor for information, examination and a rescan. Their medical history, present medication and smoking habits were recorded. The highest brachial blood pressure and the lowest systolic ankle blood pressure were recorded. A blood sample was taken in 1994 and 1998, and serum samples were stored at – 21°C until analysis.

The serum levels of cystatin C, creatinine and C-reactive protein (CRP) were measured. Serum cystatin C was analysed with the Dade Behring N Latex Cystatin C Assay (Dade Behring Diagnostics, Marburg, Germany), a fully automated particle-enhanced nephelometric immunoassay, on the Dade Behring Nephelometer II (Dade Behring Diagnostics)[11].

Serum creatinine was analysed with the Vitros CREA slide on the Vitros 950 Chemistry System (Ortho-Clinical Diagnostics, Rochester, New York, USA). CRP was measured using an ordinary commercial assay.

Creatinine clearance was estimated by means of the Cockroft–Gault formula[12]: ((140 – age) × weight (kg))/(0·825 × serum creatinine (μmol/l)).

The rate of AAA expansion was calculated as the change in anteroposterior (AP) diameter on ultrasonographic imaging during the whole observation period, transformed to annual units.

The trial was approved by the National Board of Health and the local scientific ethics committee, and was reported to the data protection authorities.

Statistical analysis was done using SPSS version 10.0 (SPSS, Chicago, Illinois, USA) to perform the Student's t test, paired t test, Wilcoxon's rank sum test, Pearson's correlational analysis, multiple linear regression analyses and receiver–operator characteristic (ROC) curve analysis.

Results

Of the 6339 men invited for screening, 4843 (76·4 per cent) attended. Of these, 191 (3·9 per cent) had an AAA. Twenty-four aneurysms (0·5 per cent) were initially over 50 mm in diameter, and these patients were referred for operation; the rest were offered annual ultrasonographic assessment. Of these, 16 were lost to follow-up during the first year. Consequently, 151 were followed for more than 1 year (mean 2·9 years). Of these, 142 patients had serum samples taken; 36 had samples taken in both 1994 and 1998. The mean(s.d.) maximal AP diameter of AAAs in the study was 34·3(4·9) mm and the mean(s.d.) annual expansion rate was 2·7(2·1) mm. The mean(s.d.) serum creatinine level was 109(25·9) μmol/l, while estimated creatinine clearance was 70·4(21·5) ml/min. The mean(s.d.) serum level of cystatin C was 1·03(0·27) mg/l.

Cystatin C is a recognized marker for the non-invasive estimation of glomerular filtration rate and a marker of early renal impairment. The present study has confirmed this by showing significant correlations between cystatin C, creatinine and creatinine clearance (*Table 1*). Furthermore, cystatin C concentration showed a negative correlation with AAA size (r = – 0·22 (95 per cent confidence interval (c.i.) – 0·59 to – 0·02)) which persisted after adjustment for renal function, smoking, diastolic blood pressure, CRP concentration and age (*Table 1*; *Fig. 1*). Cystatin C also had a negative correlation with annual aneurysm expansion rate (r = – 0·24 (95 per cent c.i. – 0·75 to – 0·05)), which persisted after adjustment for AAA size, renal function, smoking, diastolic blood pressure, CRP level and age (*Table 1*; *Fig. 2*).

Apart from serum cystatin C level, AAA size (r = 0·44) and smoking (r = 0·21) also correlated with AAA expansion, whereas serum creatinine concentration, creatinine clearance, CRP level, diastolic blood pressure and age did not.

In 36 patients, serum cystatin C concentration was measured in 1994 and 1998. The level decreased significantly between these intervals (mean(s.d.) difference – 0·15(0·7); P = 0·01). The reduction correlated significantly with initial AAA size (r = 0·58) and expansion rate (r = 0·27).

The mean duration of observation was 2·9 years. Thirty-one patients were referred for surgical assessment of an AAA that had expanded to more than 50 mm in diameter (*Table 2*). ROC curve analysis showed that the serum level of

Table 1 Correlation matrix of serum level of cystatin C, renal function and abdominal aortic aneurysm using Pearson's correlation coefficient

	Expansion rate (mm/year)	Initial AAA size (mm)	Smoker	Age (years)	Diastolic BP (mmHg)	Creatinine (μmol/l)	Cystatin C (mg/l)	Creatinine clearance (ml/min)
Cystatin C (mg/l)	– 0·24*	– 0·22*	0·03	– 0·01	– 0·17	0·65*		– 0·40*
Creatinine clearance (ml/min)	0·08	0·01	0·08	– 0·09	0·17	– 0·70*	– 0·40*	

AAA, abdominal aortic aneurysm; BP, blood pressure. *$P < 0.05$ by multiple linear regression analysis adjusting for the other variables shown

Table 2 Cystatin C, renal function and other variables in 31 patients whose abdominal aortic aneurysm expanded above 50 mm in diameter and who were referred for surgical assessment

	No surgery* ($n = 111$)	Surgery* ($n = 31$)	Mean difference†	*P*‡
AAA size (mm)	32·34(3·19)	38·83(4·88)	− 6·52 (− 8·11 to − 4·93)	0·0001§
Expansion rate (mm/year)	1·92(1·42)	4·85(2·05)	− 2·93 (− 3·59 to − 2·27)	0·0001
Cystatin C (mg/l)	1·04(0·25)	0·93(0·20)	0·11 (0·01 to 0·21)	0·035
Creatinine clearance (ml/min)	71·17(23·34)	70·47(15·38)	0·69 (− 8·34 to 9·71)	0·881
Diastolic BP (mmHg)	92·83(13·61)	94·43(13·09)	− 1·56 (− 7·21 to 4·13)	0·589

*Values are mean(s.d.); †values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm; BP, blood pressure. ‡Student's *t* test and Wilcoxon's rank sum test; §non-parametric test owing to unequal variances

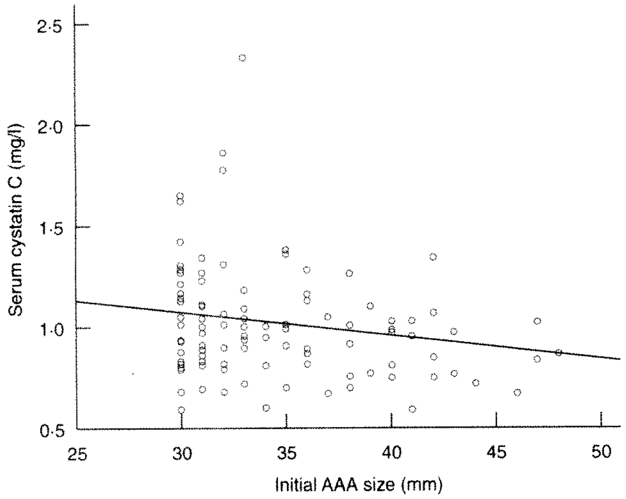


Fig. 1 Scatterplot of serum levels of cystatin C and initial abdominal aortic aneurysm (AAA) size. $r = -0{\cdot}22$ (95 per cent confidence interval $-0{\cdot}59$ to $-0{\cdot}02$) (Pearson's correlation coefficient)

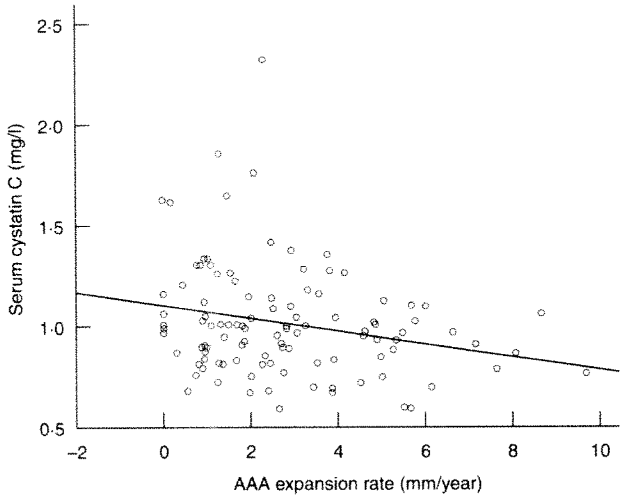


Fig. 2 Scatterplot of serum levels of cystatin C and mean annual aortic aneurysm (AAA) expansion rate. $r = -0{\cdot}24$ (95 per cent confidence interval $-0{\cdot}75$ to $-0{\cdot}05$) (Pearson's correlation coefficient)

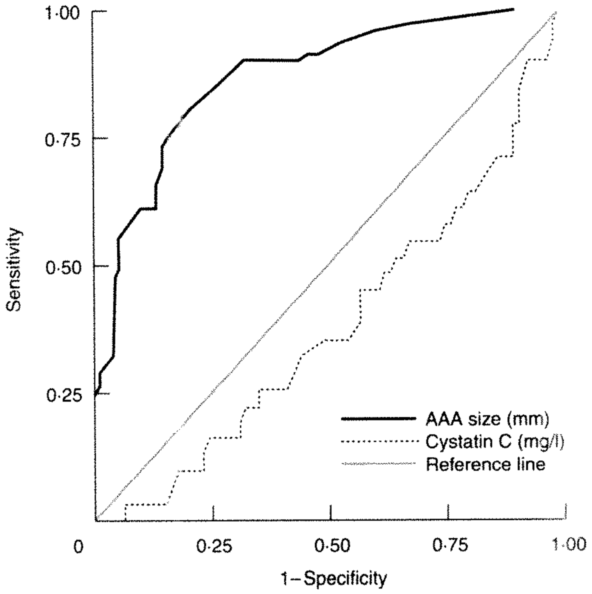


Fig. 3 Receiver–operator characteristic (ROC) curve showing the value of initial abdominal aortic aneurysm (AAA) size and serum level of cystatin C in predicting which small AAAs expand above 50 mm in diameter. Diagonal segments are produced by ties

cystatin C was predictive in such patients, with an optimal sensitivity and specificity of 61 and 57 per cent respectively (ROC curve area 0·38 (95 per cent c.i. 0·26–0·49)). The initial AAA size, however, remained more predictive for AAA expansion above 50 mm, with an optimal sensitivity and specificity both of 81 per cent (ROC curve area 0·87 (95 per cent c.i. 0·79–0·94)) (*Fig. 3*). Thus, serum cystatin C concentration seemed to be of no additional predictive value to clinicians.

Discussion

Cysteine proteases seem to be involved in the arterial wall degradation that causes AAAs. They are inhibited mainly by cystatin C. Their clinical importance was suggested by Shi *et al.*[13], who found reduced levels of cystatin C in patients with atherosclerosis and aneurysms. Aortic diameter was negatively correlated with serum cystatin C concentration, but only eight of the AAAs measured by ultrasonography were ectatic (aortic diameter greater than 25 mm) and none was frankly aneurysmal.

The present data confirmed a negative correlation with AAA size and, in addition, prospective data showed that the serum level of cystatin C was negatively correlated with AAA progression. The correlation could be the result of cystatin C being a marker of renal function or of the inflammatory process in the aorta. However, CRP and renal function were not correlated with AAA expansion, suggesting that the correlation between cystatin C and expansion was a result of the extracellular inhibition of proteases.

Because the predictive value of cystatin C was less accurate than initial AAA size, routine measurement offers no advantage.

The findings in this study suggest two potential new pharmacological interventions for small AAAs. First, *in vitro* studies have shown that administration of glucocorticoids increases the level of cystatin C[14]. Second, the secretion of cystatin C is stimulated by transforming growth factor (TGF) β_1[15]. The elastolytic properties of interferon γ-induced secretion of cathepsins from smooth muscle cells are blocked by treatment with TGF-β_1.

In conclusion, deficiency of cystatin C is associated with increased aneurysm expansion, possibly due to lack of inhibition of cysteine proteases involved in aneurysm degradation. Thus, several proteases and their inhibitors, including cystatin C, seem to be involved in the matrix degradation, in addition to metalloproteases.

Acknowledgements

The authors thank technician Lilian Christensen, nurse Anette K. Sahlholdt, Dr P. Jaeger and Dr S. Vammen for their committed assistance. The Health Department of Viborg County, The Danish Heart Foundation, The Danish National Council of Health Research, The Foundation of Research in Western Denmark, and The Foundation of Rosa and Asta Jensen are thanked for financial support.

References

1 Newby AC, Southgate KM, Davies M. Extracellular matrix degrading metalloproteinases in the pathogenesis of arteriosclerosis. *Basic Res Cardiol* 1994; 89(Suppl): 159–70.

2 Thompson RW, Parks WC. Role of metalloproteinases in abdominal aortic aneurysms. *Ann N Y Acad Sci* 1996; **800:** 157–74.

3 Carmeliet P. Urokinase-generated plasmin activates matrix metalloproteinases during aneurysm formation. *Nat Genet* 1997; **17:** 439–44.

4 Rao SK, Reddy KV, Cohen JR. Role of serine proteases in aneurysm development. *Ann N Y Acad Sci* 1996; **800:** 131–7.

5 Shi GP, Munger JS, Meara JP, Rich DH, Chapman HA. Molecular cloning and expression of human alveolar macrophage cathepsin S, an elastolytic cysteine protease. *J Biol Chem* 1992; **267:** 7258–62.

6 Reddy VY, Zhang QY, Weiss SJ. Pericellular mobilization of the tissue-destructive cysteine proteinases, cathepsin B, L, and S, by human monocyte-derived macrophages. *Proc Natl Acad Sci USA* 1995; **92:** 3849–53.

7 Abrahamson M, Barrett AJ, Salvesen G, Grubb A. Isolation of six cysteine proteinase inhibitors in human urine. Their physicochemical and enzyme kinetic properties and concentrations in biological fluids. *J Biol Chem* 1986; **261:** 11 282–9.

8 Chapman HA, Reilly JJ, Yee R, Grubb A. Identification of cystatin C, a cysteine proteinase inhibitor, as a major secretory product of human alveolar macrophages *in vitro*. *Am Rev Respir Dis* 1990; **141:** 698–705.

9 Warfel AH, Zucker-Franklin D, Frangione B, Ghiso J. Constitutive secretion of cystatin C (gamma-trace) by monocytes and macrophages and its downregulation after stimulation. *J Exp Med* 1987; **166:** 1912–17.

10 Lindholt JS, Vammen S, Juul S, Henneberg EW, Fasting H. The validity of ultrasonographic scanning as screening method for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 1999; **17:** 472–5.

11 Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II system. *Scand J Clin Lab Invest* 1999; **59:** 1–8.

12 Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. *Nephron* 1992; **62:** 249–56.

13 Shi GP, Sukhova GK, Grubb A, Ducharme A, Rhode LH, Lee RT *et al.* Cystatin C deficiency in human atherosclerosis and aortic aneurysms. *J Clin Invest* 1999; **104:** 1191–7.

14 Bjarnadottir M, Grubb A, Olafsson I. Promoter-mediated, dexamethasone-induced increase in cystatin C production by HeLa cells. *Scand J Clin Lab Invest* 1995; **55:** 617–23.

15 Grainger DJ. The serum concentration of active transforming growth factor beta is severely depressed in advanced atherosclerosis. *Nat Med* 1995; **1:** 74–9.

Original article

Methodology and reporting in studies of local recurrence after curative excision of the rectum for cancer

O. F. Dent*†, P. H. Chapuis†, E. L. Bokey† and R. C. Newland‡

*School of Social Sciences, The Faculties, Australian National University, Canberra, Australian Capital Territory, and †Department of Colon and Rectal Surgery, University of Sydney at Concord Hospital and ‡Department of Anatomical Pathology, Concord Hospital, Sydney, New South Wales, Australia

Correspondence to: Dr O. F. Dent, School of Social Sciences, The Faculties, Australian National University, Canberra, Australian Capital Territory 0200, Australia (e-mail: Owen.Dent@anu.edu.au)

Background: Widely varying rates have been reported in the extensive literature published in the English language on local recurrence after curative excision of rectal carcinoma. These variations may be attributable to differences in the case mix of pathological factors influencing recurrence, differences in surgical technique or expertise, differences in the administration of adjuvant therapy and various combinations of these. They may also arise from methodological differences among studies.

Methods: This paper reviews the adequacy of methodology and reporting in 21 recent studies of local recurrence after curative resection of rectal cancer.

Results: Many flaws in reporting and apparent inadequacies in methodology were identified. On an index of 26 criteria examined, eight studies scored no more than 8 and only three studies scored more than 11.

Conclusion: To date, the value of reports of local recurrence rates following curative excision of rectal cancer has been limited by inadequacies in documentation and methodology. Suggestions are made for preferred procedures to be followed in the reporting of future studies.

Paper accepted 22 May 2001

British Journal of Surgery 2001, **88**, 1476–1480

Introduction

Rates of local recurrence after curative excision of the rectum for cancer have varied widely among studies published in the English language over the past two decades[1,2]. These variations may be attributable to differences in the case mix of patient or pathological factors influencing recurrence, differences in surgical technique or expertise, differences in the administration of adjuvant therapy and various combinations of these. However, variations in local recurrence rates may also arise from methodological differences such as prospective *versus* retrospective data collection, diversity in patient inclusion/exclusion criteria, variability in definitions of curative surgery and local recurrence, differences in histopathological reporting, variability in the protocol for and duration of follow-up and in the ascertainment of recurrences, and differences in the method of calculation of recurrence rates.

The aims of this paper were to review the methodology and reporting among recent studies of local recurrence, to identify common flaws, and to suggest preferred procedures to be used and precautions to be taken in the conduct and presentation of such studies.

Materials and methods

A literature search of leading journals was conducted to identify studies of local recurrence after curative excision of rectal cancer published in the English language over the past two decades. The intention was not to achieve complete coverage of all recent studies or to select a random sample, but rather to provide a pool of studies for purely illustrative purposes. Over 60 examples were considered for their relevance to this purpose. This preliminary review resulted in the specification of four inclusion criteria which were thought to yield a relatively homogeneous and comparable subset of studies. The first of these criteria was that the study should present original peer-reviewed findings. Reviews and compilations of previously published work were excluded. The second criterion was that the study should report results exclusively or principally relating to patients who had been treated by surgery alone. Trials of adjuvant therapy were excluded, unless they had a surgery-only group for comparison, in which case the methods and results relating to that group were included. The third criterion was that tumours included should represent more than one histopathological stage, as stage is an important predictor of local recurrence. The fourth criterion was that the study should use the Kaplan–Meier method of time-to-event analysis[3], although not necessarily for the calculation of recurrence rates. This ensured that the authors were aware of, and capable of, using contemporary statistical methods; it also restricted studies to those published in the past decade as the Kaplan–Meier method only became widely available in statistical computing packages in the late 1980s. In a few instances, recurrence after both non-curative and curative surgery was reported; in these cases, methods and results relating to the curative group only were included. A few studies that otherwise met these criteria were excluded on the grounds that they were concerned with specialized issues such as a particular surgical technique or assessment of unusual outcomes. The selection process yielded 21 studies published between 1989 and 1998, mainly from Europe and the UK[4–24].

Results

Clinical setting, study design and recruitment of patients

All but two of the studies examined gave adequate information on the clinical setting. Ten studies were retrospective, nine were prospective, and in two the design was not specified. Recruitment of patients was consecutive in 15, random in four and unstated in two.

Exclusions

The inclusion and/or exclusion of patients with factors that may influence local recurrence was largely unstated. Ulcerative colitis as an exclusion criterion was not mentioned in 19, Crohn's disease in 20, familial adenomatous polyposis coli in 19, metachronous tumour in 20, synchronous tumour in 19, carcinoma *in situ* in 17, and emergency resection in 16. Seventeen studies did not define postoperative deaths or indicate how many had occurred or whether they had been included in the denominator of rate calculations.

Definition of the rectum

Sixteen studies did not define the rectum.

Table 1 Reporting of adjuvant therapy

	Preoperative adjuvant therapy			
	Excluded	Included	Unstated	Total
Postoperative adjuvant therapy				
Excluded	6	1		7
Included	3	2	1	6
Unstated	1	2	5	8
Total	10	5	6	21

Adjuvant therapy

The use of adjuvant therapy was not reported consistently; where reported there was considerable variation in the inclusion or exclusion of patients involved (*Table 1*). Overall nine reports did not specify whether patients had received either preoperative or postoperative adjuvant therapy, or both.

Definition of curative surgery

Twelve studies specified that the operation was deemed curative on both clinical and pathological grounds whereas one used a clinical definition only. In three of the remainder the definition was ambiguous and five gave no definition of a curative operation. The means by which the definition was put into practice was generally not well described. Eight studies did not explain how the absence of local residual tumour had been determined and only three specified the investigations used to exclude distant metastases. A detailed description of the histopathological methods was given in four studies and a brief account in four, leaving 13 with no description whatsoever. In only three instances overall was there a clear clinicopathological definition of a curative operation accompanied by a reasonably detailed account of the histopathology.

Definition of local recurrence

Only eight studies gave an explicit, unambiguous definition of local recurrence. This was defined as recurrence in the pelvis specifically in the absence of newly diagnosed distant metastases in one study, whereas in the remainder it was defined as recurrence in the pelvis, whether newly diagnosed distant metastases were absent or present. In nine studies the definition was ambiguous and four gave no definition. The method by which local recurrence was diagnosed was not described in five studies.

Follow-up

Seven reports gave a brief description of their protocol for follow-up to detect local recurrence and six gave fairly detailed accounts, including such aspects as frequency and duration of follow-up, who conducted the protocol, and the investigations used. The remaining eight gave no information on follow-up procedures. There was no mention of reasons for loss to follow-up and the number of patients lost in 13 reports.

In recurrence studies, time to recurrence is normally defined as the interval between the date of resection and the date of diagnosis of recurrence, although other bounds are conceivable. Only five studies defined explicitly the bounds on the time to recurrence.

Patients censored in Kaplan–Meier analysis would normally be those who did not have a recurrence, but who died or were lost to follow-up or were still being followed at the close of the study. However, it is possible that patients might be censored for other reasons. Only five studies stated explicitly the reasons for censoring.

As far as could be ascertained, the shortest time for which patients were followed ranged from 7 to 80 months in 13 studies. In the remainder it was unstated. Even when the shortest follow-up time was given it was frequently not clear whether this was for all patients or uncensored patients only. The average follow-up time was given in nine studies only and ranged from 29 to 100 months. Thus most of these studies were deficient or unclear with regard to the proportion of patients who had been followed for a time sufficient to allow the great majority of potential recurrences to become apparent.

Ascertainment of local recurrence in deceased patients

Only two studies specified the steps that had been taken to avoid missing local recurrence in patients who had died during follow-up.

Method of analysis

Several studies did not use the Kaplan–Meier method to calculate an overall local recurrence rate even though they had used it elsewhere in their analyses. Nine gave a crude overall rate or simply the number of recurrences. Five did not give an overall rate, but broke the analyses down into subgroup rates only. Of the seven studies in which an overall Kaplan–Meier rate was given, six gave 5-year rates ranging from 3 to 33 per cent and one a 2-year rate of 10 per cent. Only three of these seven gave a confidence interval for the rate. Although local recurrence has been shown to be stage dependent, four studies failed to give the stage distribution of tumours. Only 11 gave stage-specific local recurrence rates and only three of these were Kaplan–Meier rates.

Several studies included multivariate analyses of risk factors for local recurrence, usually applying the Cox proportional hazards method. Although this study did not aim to examine the application of multivariate analysis, it was noted that several reports did not give sufficient detail to determine whether the method had been used correctly, particularly in relation to the selection and coding of variables and the proportional hazards assumption[25].

Index of methodological adequacy

An index of methodological and reporting adequacy was constructed by scoring each study 1 or 0, according to whether it did or did not give adequate information on 26 of the criteria reviewed above, and summing the scores. The total score ranged from 5 to 19; eight studies scored no more than 8 of 26 and only three scored more than 11. The median score was 10.

Discussion

The clinical setting, study design and method of patient recruitment were described adequately in most of these studies. However, reasons for which patients may have been excluded were largely ignored. Depending on the precise aim of the study it is important that patients with characteristics which may predispose them to recurrence should be identified and their inclusion or exclusion reported explicitly. Postoperative deaths should also be accounted for.

Adjuvant therapy, given with the intention of minimizing local recurrence, clearly has the potential to be a confounding factor in outcomes. Among the studies examined the administration of adjuvant therapy was frequently not well described. Depending on a study's aim, the possible effect of including patients who received adjuvant therapy should be considered carefully. If they are included, the form of therapy and the numbers involved should be documented fully, and any effects of the therapy on outcomes should be demonstrated clearly in separate analyses.

Curative surgery and tumour staging should be defined precisely. The means of diagnosing distant metastases at the time of resection and method used to dissect the surgical specimen should both be described. The local recurrence rate may be inflated if the pathologist does not specifically seek evidence of tumour in a line of resection and stage those in whom involvement has occurred as having known residual tumour (i.e. the patient had a palliative resection). Sufficient detail should be given to allow the reader to assess how uniformly the methods and definition were applied across the patient series.

The authors agree with Marsh *et al.*[2] that the definition of local recurrence should be tumour detected in the pelvis regardless of whether or not new metastases are found elsewhere. This should be stated unambiguously.

The rate of local recurrence will be deflated to the extent that recurrences are missed because of an inadequate follow-up protocol or because patients with recurrence die from other causes or are lost to follow-up. Potential recurrences may also be missed if too great a proportion of patients is followed for too short a period to allow recurrences to become manifest. Reports should detail the follow-up protocol, including the frequency and intended duration, the investigations conducted, the criteria for a diagnosis of local recurrence, and the steps taken to rule out recurrence in deceased patients. Reasons for censoring should be stated. The minimum, maximum and median follow-up times in non-censored patients should be reported along with the proportion of patients who died, the proportion lost to follow-up and the proportion censored for any other reason. To avoid deflation of the recurrence rate the principal rate for reporting should be the 5-year rate. Preferably all non-censored patients should have been followed for at least 5 years, although a small proportion followed for a shorter time is not unacceptable.

Although a study may be focused principally on the local recurrence rate in specific subgroups, an overall Kaplan–Meier 5-year rate should be given initially, with a 95 per cent confidence interval. As tumour stage has been shown repeatedly to predict local recurrence[1], the stage distribution should be presented, along with stage-specific Kaplan–Meier rates and 95 per cent confidence intervals.

In view of the methodological and reporting inadequacies in many of the studies examined, adherence to these recommendations should lead to more standardized presentations in this field and to greater assurance that differences in recurrence rates arise out of the substantive factors being studied rather than from differences in definitions, methods and reporting. Apart from the above, many of the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement are applicable to studies of local recurrence in patient series as well as randomized controlled trials[26].

References

1 McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis* 1995; **10**: 126–32.

2 Marsh PJ, James RD, Schofield PF. Definition of local recurrence after surgery for rectal carcinoma. *Br J Surg* 1995; **82**: 465–8.

3 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Soc J* 1958; **53**: 457–81.

4 Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994; **344**: 707–11.

5 Bjerkeset T, Edna T-H. Rectal cancer: the influence of type of operation on local recurrence and survival. *Eur J Surg* 1996; **162**: 643–8.

6 Bozzetti F, Mariani L, Miceli R, Doci R, Montalto F, Andreola S *et al.* Cancer of the low and middle rectum: local and distant recurrences, and survival in 350 radically resected patients. *J Surg Oncol* 1996; **62**: 207–13.

7 Buhre LMD, Mulder NH, de Ruiter AJ, van Loon AJ, Verschueren RCJ. Effect of extent of anterior resection and sex on disease-free survival and local recurrence in patients with rectal cancer. *Br J Surg* 1994; **81**: 1227–9.

8 Dahl O, Horn A, Morild I, Halvorsen JF, Odland G, Reinertsen S *et al.* Low-dose preoperative radiation postpones recurrences in operable rectal cancer. Results of a randomized multicenter trial in western Norway. *Cancer* 1990; **66**: 2286–94.

9 de Haas-Kock DFM, Baeten CGMI, Jager JJ, Langendijk JA, Schouten LJ, Volovics A *et al.* Prognostic significance of radial margins of clearance in rectal cancer. *Br J Surg* 1996; **83**: 781–5.

10 Domergue J, Rouanet P, Daures JP, Dubois JB, Joyeux H, Solassol C *et al.* Multivariate analysis of prognostic factors for curative resectable rectal cancer. *Eur J Surg Oncol* 1989; **15**: 93–8.

11 Heald RJ, Moran BJ, Ryall RDH, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998; **133**: 894–9.

12 Holm T, Cedermark B, Rutqvist L-E. Local recurrence of rectal adenocarcinoma after 'curative' surgery and without preoperative radiotherapy. *Br J Surg* 1994, **81**: 452–5.

13 Huguier M, Chastang C, Houry S, Sima AM, Berhouet H, Chevret S. Sphincter-saving resection, or not, for cancer of the midrectum. *Am J Surg* 1997; **174**: 11–15.

14 Kessler H, Hermanek P. Outcomes in rectal cancer surgery are directly related to technical factors. *Semin Colon Rectal Surg* 1998; **9**: 247–53.

15 MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**: 457–60.

16 Mollen RMH, Damhuis RAM, Coebergh JWW. Local recurrence and survival in patients with rectal cancer, diagnosed 1981–86: a community hospital-based study in the south-east Netherlands. *Eur J Surg Oncol* 1997; **23**: 20–3.

17 Nymann T, Jess P, Christiansen J. Rate and treatment of pelvic recurrence after abdominoperineal resection and low anterior resection for rectal cancer. *Dis Colon Rectum* 1995; **38**: 799–802.

18 Pakkastie TE, Luukkonen PE, Jarvinen HJ. Anterior resection controls cancer of the rectum as well as abdominoperineal excision. *Eur J Surg* 1995; **161**: 833–9.

19 Porter GA, Soskolne CL, Yakimets WW, Newman SC.

Surgeon-related factors and outcome in rectal cancer. *Ann Surg* 1998; **227:** 157–67.

20 Rullier E, Laurent C, Carles J, Saric J, Michel P, Parneix M. Local recurrence of low rectal cancer after abdominoperineal and anterior resection. *Br J Surg* 1997; **84:** 525–8.

21 Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; **336:** 980–7.

22 Treurniet-Donker AD, van Putten WLJ, Wereldsma JCJ, Bruggink EDM, Hoogenraad WJ, Roukema JA *et al.* Postoperative radiation therapy for rectal cancer. An interim analysis of a prospective, randomized multicenter trial in The Netherlands. *Cancer* 1991; **67:** 2042–8.

23 Tschmelitsch J, Kronberger P, Prommegger R, Reibenegger G, Glaser K, Bodner E. Survival and local recurrence after anterior resection and abdominoperineal excision for rectal cancer. *Eur J Surg Oncol* 1995; **21:** 640–3.

24 Volpe C, Rodriguez-Bigas M, Petrelli NJ. Wide perineal dissection and its effect on local recurrence following potentially curative abdominoperineal resection for rectal adenocarcinoma. *Cancer Invest* 1996; **14:** 1–5.

25 Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med* 1993; **118:** 201–10.

26 Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; **285:** 1987–91.

Original article

Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence

D. F. Altomare, G. Dodi*, F. La Torre†, G. Romano‡, E. Melega* and M. Rinaldi

Department of General Surgery and Liver Transplantation, University of Bari, Bari, *Section of Surgical Clinic II, Department of Surgical and Oncologic Sciences, University of Padua, Padua, †III Surgical Clinic, University of Rome 'La Sapienza', Rome and ‡Department of General Thoracic and Vascular Surgery, University Federico II, Naples, Italy

Correspondence to Dr D. F. Altomare, Department of Emergency and Organ Transplantation, Section of General Surgery and Liver Transplantation, Policlinico, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy (e-mail altomare@clichiru.uniba.it)

Background: A new prosthetic device, the Acticon^{TM} artificial anal sphincter, has recently been introduced for treating severe faecal incontinence. The results of this procedure in 28 patients are presented.

Methods: The patients underwent operation for severe faecal incontinence in four Italian university hospitals and patients were reviewed after a median follow-up of 19 (range 7–41) months.

Results: Early infections occurred in four patients, requiring removal of the device in three. Dehiscence of the perineal wound occurred in nine patients. After activation of the device, the cuff had to be removed in a further four patients (for rectal erosion in two, anal pain in one and late infection in one). The cuff was accidentally broken in one patient. A new anal cuff was repositioned successfully in two patients. Overall, five patients had complete removal of the device and two removal of the cuff only. Twenty-one patients available for long-term evaluation had a major improvement in faecal continence. Median resting anal pressure increased from 27 mmHg before surgery to 32 mmHg after operation. Preoperative squeeze pressure was 42 mmHg while maximum postoperative anal pressure with the activated device was 67 mmHg. The median American Medical System incontinence score decreased significantly from 98·5 to 5·5 ($P < 0{\cdot}001$). Similar figures were observed using the Continence Grading Scale (from 14·9 to 2·6; $P < 0{\cdot}001$). Twelve patients developed symptoms of obstructed defaecation while two patients complained of anal pain.

Conclusion: Improved continence was achieved after neosphincter implantation in three-quarters of the patients. Early infection and rectal erosion, together with difficulty in evacuating, are still major concerns with this technique.

Paper accepted 14 June 2001

British Journal of Surgery 2001, 88, 1481–1486

Introduction

Treatment of severe faecal incontinence is a difficult challenge for colorectal surgeons. However, the introduction of new sophisticated devices to replace the non-functioning anal sphincter offers patients suffering from this disabling condition a better chance of achieving continence. Owing to the development of an electrostimulated gracilis neosphincter technique[1] and, more recently, of an artificial anal sphincter[2] there are few patients with faecal incontinence who cannot be treated without a reassuring prospect of success.

At present, the indications for these two treatment methods overlap widely and the choice of operation should be based on considerations such as cost, chance of success and risk of complications, and surgical aspects such as length of operating time, complexity of the procedure and need for a long learning curve.

Recent reports indicate that the artificial anal sphincter is reasonably successful in treating patients with end-stage faecal incontinence[3–7] and is comparable to graciloplasty[8]. However, the risk of infection and erosion of the device into the anal canal remain problematic. This study is a review of the experience gained with this new device by an Italian group of colorectal surgeons; the results were analysed to identify any technical details that could be bettered when planning a prospective multicentre study.

Patients and methods

Patient with severe faecal incontinence not amenable to conservative treatment and who were able to understand and manage the device were selected for the procedure. External anal sphincter lesions that could be treated by sphincteroplasty were excluded on the basis of the patient's history, confirmed by endoanal ultrasonography. Only patients with at least 6 months of follow-up after sphincter activation were considered in this evaluation.

Twenty-eight female patients with a mean age of 58 (range 35–79) years affected by severe faecal incontinence lasting more than 1 year (median 9 (range 1–49) years) entered the study after given written informed consent. All were instructed carefully about the device with the aid of a video demonstration. All were treated at Italian university hospitals, 12 in Padua, six in Bari, five in Rome and five in Naples. The cause of incontinence was idiopathic in 14 patients, obstetric in six, neurological in four, postanal surgery in three and congenital malformation in one. In 11 patients there was associated complete (full thickness) rectal prolapse; this was treated before implantation of the artificial sphincter by sacral rectopexy (Wells' operation) in five patients and by perineal rectosigmoidectomy (Altemeier operation) in one patient. The remaining five patients (operated in Padua) underwent artificial anal sphincter implantation without treatment of the prolapse. Two patients suffered from liver cirrhosis with a high risk of haemorrhage. One had associated urinary incontinence which had been treated with Burch's operation. Another patient developed severe symptoms of systemic sclerosis after implantation of the artificial sphincter. Seven patients had undergone anal surgery previously (haemorrhoidectomy in two, postanal repair in one, local excision of cancer in one, sphincteroplasty in two and Altemeier operation in one).

All patients underwent preoperative and postoperative anal manometry to evaluate the mean resting anal pressure and the length of the high-pressure zone before and after implantation of the artificial anal sphincter. The preoperative squeeze pressure and the maximal anal pressure with the activated device were also evaluated. The severity of incontinence was graded according to two scoring systems: the American Medical System (AMS) score[4] and the Continence Grading Scale (CGS)[9]. In a group of 14 patients perceived changes in quality of life (QOL) were assessed using a specially constructed questionnaire provided by the AMS, a slightly modified version of which has subsequently been validated[10]. Postoperative assessments were made at least 6 months after activation of the device.

Mechanical preparation of the colon was achieved by administering osmotic solutions and enemas the day before surgery. Nineteen patients also underwent rectal wash-out with dilute iodinated solution just before the operation. Vaginal preparation with antibiotic vaginal suppositories and intraoperative disinfection was performed in 18 patients. Twenty patients received combined antibiotic prophylaxis with metronidazole and cephalosporins. Eight had only cephalosporins. A protective ileostomy was fashioned in one patient.

The patients were placed in the lithotomy position under general anaesthesia. To create a tunnel around the anus by blunt dissection, the rectovaginal septum was opened in all but one patient, who was subjected to a double perianal incision approach. The operation to implant the Acticon Neosphincter™ artificial bowel sphincter (American Medical Systems, Minneapolis, Minnesota, USA) was then performed as described by Lehur *et al.*[11].

The size of the anal cuff was decided for each patient by the surgeon, on the basis of evaluation of the space available around the anorectum. A cuff 2·9 cm wide was used in 16 patients and one 2 cm wide in the remaining 12. The pressure within the balloon was between 81 and 90 mmHg in seven patients, between 91 and 100 mmHg in 20, and between 101 and 110 mmHg in one. The length of the band was 9 cm in one patient, 10 cm in three, 11 cm in seven, 12 cm in seven, 13 cm in six and 14 cm in the remaining four patients. The mean duration of operation was 145 (range 90–250) min. Antibiotic prophylaxis was continued after operation for a median of 4 (range 1–7) days and at least one dressing was applied per day. Patients operated in Padua also received loperamide after operation to postpone defaecation and so prevent early contamination of the wound.

The implanted device was activated at least 2 months after the operation to ensure complete wound healing and consolidate the prevesical space made to house the pressure balloon.

Statistical analysis

The Wilcoxon rank sum test and Fisher's exact test were used to compare preoperative and postoperative results. $P < 0{\cdot}05$ was considered to be statistically significant.

Results

The median follow-up was 19 (range 7–41) months. Early infection of perineal and abdominal wounds occurred in three patients and of the perineal wound only in one patient, requiring removal of the whole device in three patients. One perineal wound infection was treated conservatively, but 2 months later the cuff eroded the perianal skin and had to be removed together with the pump and balloon. One

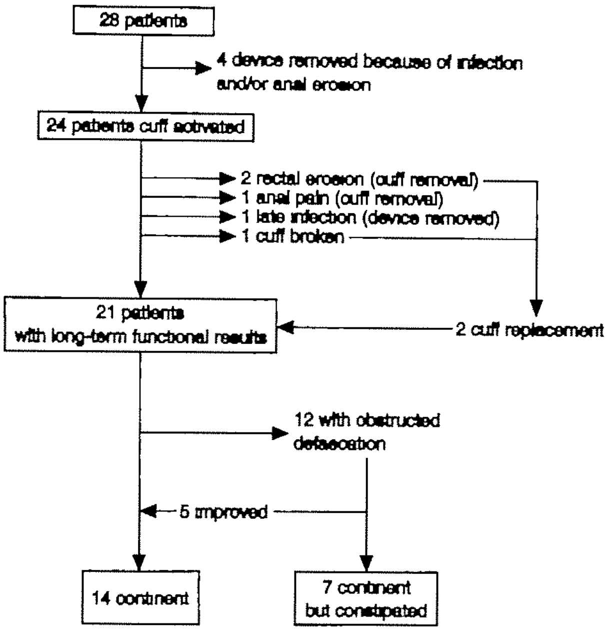

28 patients
4 device removed because of infection and/or anal erosion
24 patients cuff activated
2 rectal erosion (cuff removal)
1 anal pain (cuff removal)
1 late infection (device removed)
1 cuff broken
21 patients with long-term functional results
2 cuff replacement
12 with obstructed defaecation
5 improved
14 continent
7 continent but constipated

Fig. 1 Flow chart showing the clinical outcome of 28 incontinent patients submitted to artificial anal sphincter implantation

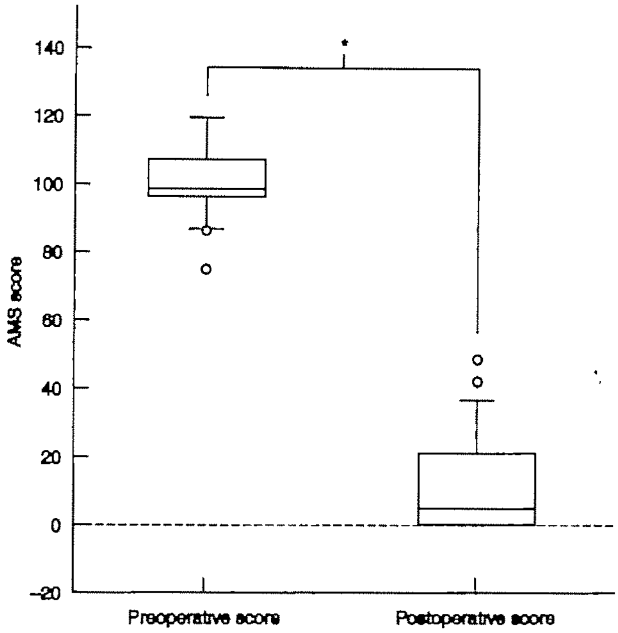


Fig. 2 Changes in severity of faecal incontinence, measured by American Medical System (AMS) score, after artificial anal sphincter implantation. Circles indicate range limits, short horizontal lines the 10th and 90th percentile, horizontal lines within boxes the median values and the boxes denote values between the 25th and 75th percentile. $^*P < 0{\cdot}001$ (Wilcoxon rank sum test)

haematoma occurred at the site of implantation of the balloon and required surgical drainage. Superficial dehiscence of the perineal wound occurred in nine patients. Surgical treatment with a rotating cutaneous flap was needed in two and with direct repair in one. No case of perineal skin dehiscence caused subsequent removal of the cuff.

After activation of the device, the cuff had to be removed in a further four patients, for rectal erosion in two (one of whom had an Altemeier procedure for rectal prolapse), and pain or late infection in the others. In one patient a new anal cuff was repositioned successfully. Another patient required substitution of the pressure balloon because of the low pressure delivered at the anal cuff. During follow-up one further patient had the anal cuff substituted owing to accidental breakage. Overall, five patients had complete removal of the device and two removal of the cuff only. In one patient the system was left deactivated because of anal pain. The clinical outcome is summarized in *Fig. 1*. Twenty-one patients were available for long-term clinical evaluation. All had a major improvement in continence to liquid and solid stools, with a consequent improvement in QOL. The median QOL score in 14 patients fell from a preoperative value of 65 to 8 per cent after activation of the device ($P < 0{\cdot}001$).

The median AMS incontinence score decreased significantly from 98·5 (range 75–120) to 5·5 (range 0–49) after neosphincter implantation ($P < 0{\cdot}001$) (*Fig. 2*). Similar figures were observed using the CGS score: from 14·9 (range 11–20) to 2·6 (range 0–6) ($P < 0{\cdot}001$). Twelve patients developed symptoms of obstructed defaecation and seven needed daily enemas to evacuate. Manual evacuation of a faecaloma was occasionally needed in three patients. In two of these patients, the cuff was deactivated since defaecation became the major problem instead of incontinence. Two patients complained of anal pain, one of whom had the anal cuff removed. The other patient, who had an operation for complete rectal prolapse with the Altemeier procedure, subsequently developed a rectal erosion and was not therefore included in the functional evaluation; the same patient also complained of painful dyspareunia. Four of the 11 patients with rectal prolapse had the device totally or partially removed for infection or mucosal erosion, two who underwent surgical repair of the prolapse and two without prolapse repair. Furthermore, one patient in each group developed symptoms of severe obstructed defaecation. Therefore, only two of 12 patients with some symptoms of postoperative obstructed defaecation had a rectal prolapse before implantation of the artificial anal sphincter. Seven of 12

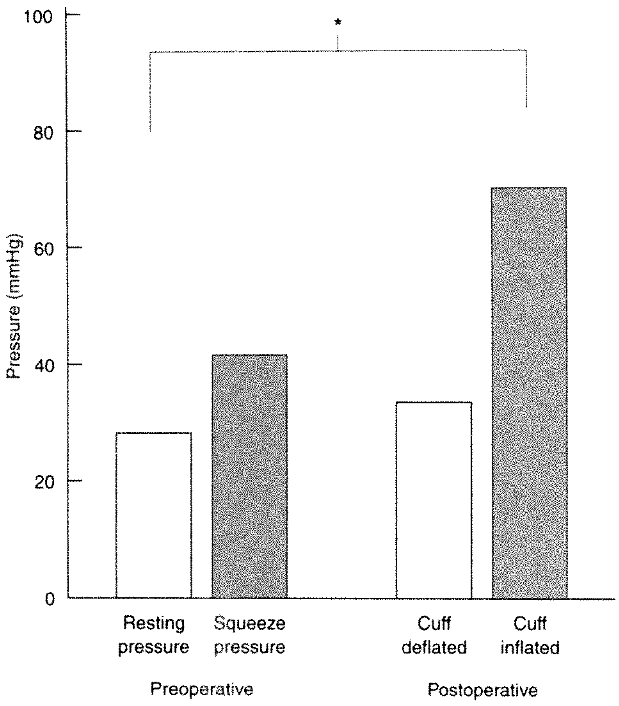


Fig. 3 Changes in anal pressure before and after artificial anal sphincter implantation. $^*P < 0{\cdot}001$ (Wilcoxon rank sum test)

patients with symptoms of obstructed defaecation had an anal cuff 2·9 cm wide. Statistical analysis showed that this type of cuff was significantly associated with obstructed defaecation ($P = 0{\cdot}015$, Fisher's exact test).

Manometric results

Median resting anal pressure was 27 (range 5–71) mmHg before operation and 32 (range 11–59) mmHg after surgery with the device inactivated (P not significant). The preoperative squeeze pressure was 42 (range 11–110) mmHg while the maximum postoperative anal pressure with the device activated was 67 (range 14–145) mmHg; this value was significantly higher than the preoperative resting pressure ($P < 0{\cdot}001$) but not the preoperative squeeze pressure ($P = 0{\cdot}061$) (*Fig. 3*). The length of the high-pressure anal zone did not change significantly.

Discussion

Analysis of the results of this multicentre experience confirms that the Acticon™ artificial anal sphincter is an effective tool for treating end-stage faecal incontinence. The patients who could potentially benefit from this procedure are mostly those with idiopathic faecal incontinence, but even patients with severe sphincter damage, especially when associated with pudendal neuropathy, could be good candidates for this procedure[12,13].

Several technical aspects of the operation can probably be improved. Anterior perineal access to position the anal cuff is the most difficult stage of the procedure and is associated with a relatively high percentage of wound dehiscence, which can sometimes result in infection of the cuff. This approach caused skin dehiscence in nine of 28 patients in this study. Other centres have reported a wound dehiscence rate ranging between 8 and 17 per cent[4,7,14]. This observation has led the present authors to discard this approach in favour of the more simple double lateral perianal approach, which affords easier creation of a tunnel around the anus by blunt dissection.

Further efforts should be made to establish better methods for preventing infection, including more generous, prolonged antibiotic prophylaxis, local procedures including intraoperative rectal wash-out with iodinated solutions, and the suture of a finger glove to the anus to prevent accidental passage of faeces from the rectum. This also enables the surgeon to insert a finger into the rectum during the perianal manoeuvres without causing gross contamination.

Acticon™ implantation carries a failure rate of about 25 per cent due to technical problems and infection but, provided that these are overcome, the device works satisfactorily, restoring continence and improving QOL in all patients who completed the questionnaire. Although surgical experience with this new device in the field of faecal incontinence is still in its infancy, the overall results are similar, if not better, than those obtained in the two recent multicentre trials with electrostimulated graciloplasty[15,16], which has up to now been the last resort for such cases of incontinence.

The incidence of complications requiring definitive explant of the device is similar to that reported in other series with a comparable number of patients. Lehur *et al.*[4] reported seven device explants in 24 patients and Devesa *et al.*[14] ten in 39 patients. However, it must be noted that almost all the patients who overcame the risk of infection and skin or rectal erosion achieved full continence to faeces.

A major concern with this device is the risk of ensuing obstructed defaecation, which can in some cases lead to faecal impaction requiring manual evacuation. Over half of the present patients complained of some degree of difficulty in defaecating and one-third had to resort to daily enemas. Similar problems were described by Lehur *et al.*[4] and by Devesa *et al.*[14], who reported obstructed defaecation in 29 and 17 per cent of patients respectively. This problem is not new in surgery for incontinence using neoanal sphincters and it is a common complaint in patients operated with graciloplasty[17]. In some of these patients the problem may be so severe that an association of graciloplasty with an antegrade colonic conduit was suggested by Williams *et al.*[18]. It is not always easy to identify the reason for this, although in some cases an undetected rectocele can be the cause[19].

With regard to the artificial anal sphincter, too wide and stiff a cuff could be responsible for obstructed defaecation. In this study there was greater difficulty in defaecation when a 2·9-cm cuff was implanted rather than a 2·0-cm cuff. Anal stenosis was excluded in all cases, but some functional disturbances of defaecation (rectal intussusception) were demonstrated in two patients by postoperative dynamic defaecography. Careful preoperative investigations should be planned with the specific purpose of identifying patients at risk of obstructed defaecation.

The management of a concomitant full-thickness rectal prolapse is still a matter for debate. This condition has been considered a relative contraindication to this technique, but correction of the prolapse before implantation can restore the anatomy of the anorectum. However, some surgeons in this study preferred to treat the prolapse with sacral rectopexy while implanting the artificial sphincter, while others believed that the implantation procedure itself should suffice to correct both rectal prolapse and incontinence. This matter requires further study in larger series of patients. Surgery for rectal prolapse, especially with full rectal mobilization, has been blamed for causing postoperative obstructed defaecation, although no such association was found in the present study. It is probable that perineal rectosigmoidectomy (the Altemeier procedure) should be avoided as contact between the sutures and the anal cuff may predispose to rectal erosion.

A comparison between artificial anal sphincter and electrostimulated graciloplasty in end-stage faecal incontinence is still premature, although artificial anal sphincter implantation is easier and quicker to perform, causes less postoperative pain and does not require a long training period for muscle education. Both techniques are burdened with a high complication rate and risk of some functional disturbance. Finally, although in Italy the device is still more expensive than the implantable pulse generator (Interstim®; Medtronic, Minneapolis, Minnesota, USA) and wire electrodes required for graciloplasty (€11 880 *versus* 9297), in the long term it could have a lower cost because there is no need for battery replacement. However, a correct analysis of the costs should also include replacement of parts of the artificial anal sphincter or reoperation for infection or mechanical failure, as occurred in some patients in this study. A longer follow-up of larger series is planned, to obtain a more reliable evaluation of this new device.

Acknowledgements

The authors acknowledge the active participation in this study of Professor M. Lise, Professor V. Memeo, Professor A. Montori and Dr A. Novi. They thank Professor P. A. Lehur for teaching the technique and Ms M. V. C. Pragnell for help in revising the manuscript.

References

1 Williams NS, Hallan RI, Koeze TH, Pilot MA, Watkins ES. Construction of a neoanal sphincter by transposition of the gracilis muscle and prolonged neuromuscular stimulation for the treatment of faecal incontinence. *Ann R Coll Surg Engl* 1990; **72**: 108–13.

2 Christiansen J, Sparso B. Treatment of anal incontinence by an implantable prosthetic anal sphincter. *Ann Surg* 1992; **215**: 383–6.

3 Wong WD, Jensen LL, Bartolo DC, Rothenberger DA. Artificial anal sphincter. *Dis Colon Rectum* 1996; **39**: 1345–51.

4 Lehur PA, Roig JV, Duinslaeger M. Artificial anal sphincter. prospective clinical and manometric evaluation *Dis Colon Rectum* 2000; **43**: 1100–6.

5 Vaizey CJ, Kamm MA, Gold DM, Bartram CI, Halligan S, Nicholls RJ. Clinical, physiological, and radiological study of a new purpose-designed artificial bowel sphincter. *Lancet* 1998; **351**: 105–9.

6 Dodi G, Melega A, Masin A, Infantino A, Cavallari F, Lise M. Artificial bowel sphincter (ABS) for severe faecal incontinence: a clinical and manometric study. *Colorectal Dis* 2000; **2**: 207–11.

7 O'Brien PE, Skinner S. Restoring control: the Acticon Neosphincter artificial bowel sphincter in the treatment of anal incontinence. *Dis Colon Rectum* 2000; **43**: 1213–16.

8 Altomare DF. Muscle transposition for fecal incontinence. Graciloplasty. In: Romano G, ed. *Diagnosis and Treatment of Fecal Incontinence* Naples: Idelson-Gnocchi, 2000: 151–62.

9 Jorge JMN, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; **36**: 77–97.

10 Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG *et al.* Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. *Dis Colon Rectum* 2000; **43**: 9–17.

11 Lehur PA, Michot F, Denis P, Grise P, Leborgne J, Teniere P *et al.* Results of artificial sphincter in severe anal incontinence. Report of 14 consecutive implantations. *Dis Colon Rectum* 1996; **39**: 1352–5.

12 Romano G, Belli G, Novi A, Esposito P, Farella Acaggiano L. Sphincteroplasties. In: Romano G, ed. *Diagnosis and Treatment of Fecal Incontinence*. Naples: Idelson-Gnocchi, 2000: 129–42

13 Madhoff RD, Baeten CGMI, Christiansen J, Rosen HR, Williams NS, Heine JA *et al.* Standards for anal sphincter replacement. *Dis Colon Rectum* 2000; **43:** 135–41.

14 Devesa JM, Hervàs PL, Sánchez S. Artificial anal sphincter: functional results and complications of a large personal series. *Colorectal Dis* 2000; **2**(Suppl I): 13 (Abstract).

15 Mander BJ, Wexner SD, Williams NS, Bartolo DC, Lubowski DZ, Oresland T *et al.* Preliminary results of a multicentre trial of the electrically stimulated gracilis neoanal sphincter. *Br J Surg* 1999; **86:** 1543–8.

16 Madoff RD, Rosen HR, Baeten CG, LaFontaine LJ, Cavina E, Devesa M *et al.* Safety and efficacy of dynamic muscle plasty for anal incontinence: lessons from a prospective, multicenter trial. *Gastroenterology* 1999; **116:** 549–56.

17 Seccia M, Menconi C, Balestri R, Cavina E. Study protocols and functional results in 86 electrostimulated graciloplasties. *Dis Colon Rectum* 1994; **37:** 897–904.

18 Williams NS, Hughes SF, Stuchfield B. Continent colonic conduit for rectal evacuation in severe constipation. *Lancet* 1994; **343:** 1321–4.

19 Altomare DF, Rinaldi M, Pannarale O, Martinelli E, Palasciano N, Memeo V. Vaginal repair of rectocele after dynamic graciloplasty for fecal incontinence due to imperforate anus. *Int J Colorectal Dis* 1996; **11:** 243–5.

Original article

Long-term effects of stapled haemorrhoidectomy on internal anal function and sensitivity

D. F. Altomare, M. Rinaldi, P. L. Sallustio, P. Martino*, M. De Fazio and V. Memeo

Department of Emergency and Organ Transplantation, Section of General Surgery and Liver Transplantation and *Section of Urology and Renal Transplantation, University of Bari, Bari, Italy

Correspondence to: Dr D. F. Altomare, Department of Emergency and Organ Transplantation, Section of General Surgery and Liver Transplantation, Policlinico, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy (e-mail: altomare@clichiru.uniba.it)

Background: Stapled haemorrhoidectomy is gaining wide acceptance but there is still some concern about the risk of injury to the internal anal sphincter (IAS). IAS function and morphology, and anal canal sensitivity were studied prospectively in patients undergoing this operation.

Methods: Twenty patients (11 women; mean age 43 years) with stage III haemorrhoids entered the study. All underwent preoperative anorectal manometry, rectoanal inhibitory reflex (RAIR) testing and three-dimensional transanal ultrasonography. A test of anal sensation was administered to evaluate ability to discriminate between air and warm water. All the investigations were repeated 6 months after the operation.

Results: The mean(s.d.) maximal resting pressure was 87(30) mmHg before surgery and 81(20) mmHg afterwards (*P* not significant). The maximal squeeze pressure did not change after operation (178(43) *versus* 174(60) mmHg). The RAIR showed the same features in 19 of 20 patients before and 18 of 20 after operation. Three-dimensional ultrasonography demonstrated no changes in the width of the IAS (mean(s.d.) 2·1(4) mm before and 2·1(3) mm after surgery). The ability of the anal mucosa to discriminate air from warm water improved in five patients. Continence scores did not differ significantly after 6 months.

Conclusion: Stapled haemorrhoidectomy does not affect the function and morphology of the IAS in the long term. The sensitivity of the anal canal can improve in patients with preoperative sensory impairment.

Presented in part to the joint meeting of the Italian Society of Coloproctology and Unità di Colou Proctologia Club, Verona, Italy, September 2000

Paper accepted 20 June 2001

British Journal of Surgery 2001, **88**, 1487–1491

Introduction

Stapled haemorrhoidectomy for prolapsed haemorrhoids or rectal mucosal prolapse is gaining wide acceptance among coloproctologists in Europe[1–4]. Several prospective randomized trials have demonstrated that, after short and medium follow-up, this new technique is as effective as the standard Milligan–Morgan operation but better tolerated by patients owing to less postoperative pain and an earlier return to work[5–8]. However, some doubts persist among colorectal surgeons, because of concern about the risk of injuring the internal and external anal sphincters, causing impaired anal continence[9]. Not only could introduction of a 33-mm stapler cause excessive anal stretching but stapler firing of the mucosal purse-string could entrap smooth muscle fibres of the internal anal sphincter (IAS).

This prospective study aimed to evaluate any changes occurring in anorectal physiology and sensitivity of the anal canal after stapled haemorrhoidectomy.

Patients and methods

Twenty consecutive patients (11 women; mean(s.d.) age 43(14) median 38 (range 25–67) years) with stage III haemorrhoids entered the study after giving informed consent. Exclusion criteria included any gross disturbance of anal continence, pre-existing anal sphincter lesions at transanal ultrasonography, age over 70 years, diabetes or

Table 1 American Medical Systems faecal incontinence score

How often during the past 4 weeks did you experience	Never	Rarely	Sometimes	Weekly	Daily	Several times daily
Accidental bowel leakage of gas?	0	1	7	13	19	25
Minor bowel soiling or seepage?	0	31	37	43	49	55
Significant accidental leakage of liquid stool?	0	61	73	85	97	109
Significant accidental leakage of solid stool?	0	67	79	91	103	115
Has this accidental leakage affected your lifestyle?	0	1	2	3	4	5

Never, no episodes in the past 4 weeks; rarely, one episode in the past 4 weeks; sometimes, more than one episode in the past 4 weeks but less than one per week; weekly, one or more episodes per week but less than one per day; several times daily, more than one episode per day. The score is calculated by adding the highest value for the type of incontinence to a 0–5-point evaluation of lifestyle so that it can range from 0 (normal continence) to a maximum of 120 (maximal incontinence with maximal disturbance of lifestyle)

Table 2 Continence Grading Scale

Type of incontinence	Never	Rarely	Sometimes	Usually	Always
Solid stools	0	1	2	3	4
Liquid stools	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4

Never, no episodes of incontinence; rarely, less than one per month; sometimes, more than one episode per month but less than one per week; usually, one or more episodes per week but less than one per day; always, more than one episode per day. The score is calculated by adding the highest value for the type of incontinence to a 0–4-point evaluation of lifestyle so that it can range from 0 (normal continence) to a maximum of 20 (maximal incontinence with maximal disturbance of lifestyle)

neurological disease. All patients underwent preoperative evaluation by anoscopy and colonoscopy.

With the patient lying in the left lateral position with the hips flexed, anorectal manovolumetry was performed by one operator (P.L.S.) using a probe incorporating three coaxial microtransducers (Gaeltec, Dunvegan, UK) with a 4-mm diameter, inserted through the anus after bowel preparation and connected to a computerized manometric system (Griffon, Albyn Medical, Dingwall, UK) with dedicated software (Phoenix, Dingwall, UK). The rectoanal inhibitory reflex (RAIR) was elicited by step air inflation of a low-compliance latex balloon placed in the rectal ampulla. The minimum volume required to elicit the reflex, its latency and duration were calculated according to a technique described elsewhere[10].

Three-dimensional transanal ultrasonography was performed by one operator (P.M.) using a Voluson 530D three-dimensional CFM ultrasound scanner (Kretz Technik, Zipf, Austria) with a multiplanar volumetric transanal probe with a wide band (5–10 MHz). Patients were prepared with an enema 1 h before the examination, which was performed in Sims' position. Three-dimensional reconstruction was carried out after transverse and coronal plane scanning.

Any impairment of faecal continence was graded according to two scoring systems: the American Medical System (AMS) score[11] (*Table 1*) and the Continence Grading Scale (CGS)[12] (*Table 2*). Although neither method has yet been validated prospectively, they are the most widely accepted in the literature at present.

A test of anal sensation was administered to evaluate patients' ability to discriminate between air and warm water[13]. A flexible anal probe consisting of three nylon catheters welded together, with side openings 2 cm apart, was inserted into the middle anal canal. One of the catheters was connected to a syringe filled with water at 37°C and another to an air-filled syringe. The content of the syringes was rapidly injected into the anal canal and the patient was asked to identify whether it was air or water. Some 2 ml of water and 4 ml of air were injected randomly five times in each patient. At least eight of ten correct responses were considered to indicate full anal discriminatory ability, between five and seven indicated imperfect discrimination, and less than five represented poor discrimination.

All anal physiology tests were repeated 6 months after surgery. Transanal ultrasonography was repeated once, at least 3 months after the operation.

The patients were operated by the same surgical team (D.F.A., M.R.) with a PPH 01 kit (Ethicon EndoSurgery, Cincinnati, Ohio, USA) using a standardized technique, under epidural anaesthesia with hyperbaric bupivacaine chlorhydrate. After introduction of the transparent anoscope and the anal valve of the kit, double purse-strings 2 cm apart were prepared in the rectum, with 2/0 polypropylene sutures, at least 3 cm from the dentate line. The two mucosal purse-strings were fashioned without administering a submural injection. The stapler was introduced completely opened, the sutures were tied on the shaft and traction was exerted through the holes of the

Table 3 Anal manometry before and 6 months after stapled haemorrhoidectomy in 20 patients

	Before operation	After operation
Maximum resting pressure (mmHg)	87(30)	81(20)
Mean resting pressure (mmHg)	57(20)	54(15)
Maximum squeeze pressure (mmHg)	178(43)	174(60)
Mean squeeze pressure (mmHg)	116(40)	109(40)

Values are mean(s.d.). There were no significant differences between preoperative and postoperative values

Table 4 Rectoanal inhibitory reflex features before and 6 months after stapled haemorrhoidectomy in 20 patients

	Before operation	After operation
RAIR present	19 of 20	18 of 20
Volume required (ml)	29(15)	31(15)
Latency (s)	6·3(1·5)	5·7(1·8)
Duration (s)	17(6)	15(6)
Pressure decrement (mmHg)	35(3)	29(1)

Values are mean(s.d.). RAIR, rectoanal inhibitory reflex. There were no significant differences between preoperative and postoperative values

stapler. The stapler was then closed and fired. Careful inspection of the suture line was carried out to check for any bleeding. A 24-Fr Foley catheter was left in the rectum for 6–12 h to ensure early detection of postoperative bleeding which could be stopped by moderate traction on the catheter after balloon inflation. All resected specimens were sent to the pathologist for histological evaluation.

Statistical analysis

Data are expressed as mean(s.d.) unless otherwise indicated. Comparison between preoperative and postoperative evaluations was performed using Student's *t* test for paired data. $P < 0·05$ was considered statistically significant.

Results

There was one instance of postoperative bleeding, which was stopped by traction for 24 h on the rectal Foley catheter with the balloon inflated with 30 ml of water. Two patients complained of postoperative pain that required intramuscular analgesics for 3 days, while the others received oral analgesia for 24–48 h after operation. Median follow-up was 12 (range 8–15) months.

All resected specimens contained columnar epithelium without any transitional or multilayer zones. Sixteen specimens contained smooth muscle fibres, presumably belonging to the low rectum.

Anal continence

All patients had full anal continence before operation except one who complained of rare episodes of leakage (CGS 3). In the early postoperative period (within 1 month) seven patients experienced some form of minor incontinence (mainly urgency) which included two episodes of faecal incontinence in one patient. Anal manometric variables were within the normal laboratory range in all patients. The mean CGS was 0·2 before operation, 0·4 after 3 months and 0·1 after 6 months; the mean AMS score was 2·2 before surgery, 9·7 at 3 months and 1·3 at 6 months after surgery. After at least 6 months all the patients were reviewed and faecal continence was found to have returned to normal in all cases. Only one patient still complained of some sensations of urgency to defaecate but no episodes of incontinence. This patient was treated successfully with biofeedback training.

Manometry

The results of anal manometry and RAIR data are summarized in *Tables 3* and *4*. There were no statistically significant differences between preoperative and postoperative values. The length of the high-pressure zone was 34·4(11·0) mm before and 32·4(7·0) mm after operation (*P* not significant).

Endoanal ultrasonography

Three-dimensional ultrasonography was carried out before and after operation in all 20 patients and showed no lesions or fragmentation of the IAS, nor changes in the width of the IAS (2·1(4·0) mm before and 2·1(3·0) mm after surgery).

Anal sensitivity

Before operation, the ability of the anal mucosa to discriminate air from warm water was normal in 13 patients, imperfect in four and poor in the remaining three. At least 3 months after surgery the latter three patients were all fully able to discriminate air from warm water, two patients with imperfect sensation improved, one remained unchanged and in one the discriminatory ability of the mucosa worsened. The other patients maintained a normal degree of discriminatory anal sensation. Overall, 16 of 20 patients had normal anal sensitivity after operation.

Discussion

In a recent commentary on the first two randomized trials of stapled *versus* Milligan–Morgan haemorrhoidectomy, Fazio[9] listed a number of points indicating how the effectiveness of stapled haemorrhoidectomy should be further investigated. One of these was prospective objective assessment of anal sphincter function, with long-term follow-up using a validated continence scoring system. Although the stapled operation for prolapsed haemorrhoids has been demonstrated to be as effective as the standard Milligan–Morgan operation, in terms of a similar complication and success rate but featuring less postoperative pain and an earlier return to work, some scepticism still persists owing to the absence of long-term results and because there is a risk of damage to the anal sphincter. Several authors have pointed out that simply introducing the stapler through the anus could cause IAS lesions[14], while inadvertent inclusion of muscle fibres in the stapler could directly damage the IAS. However, surgery for haemorrhoids is not entirely free from such functional complications; the effects of traditional haemorrhoidectomy (Milligan–Morgan), in particular, have been investigated thoroughly by several authors. In 1982, in a prospective series of 24 patients who had the Milligan–Morgan operation for third-degree haemorrhoids, Read *et al.*[13] found a significant decrease in basal and squeezing anal pressure compared with preoperative values. Although these values remained within the normal range, two patients developed incontinence to liquid stool. Similar findings were demonstrated by Ho and Tan[15] using ambulatory anorectal manometry. These effects were independent of additional surgical manoeuvres such as lateral internal sphincterotomy or anal stretching, which are sometimes added to the main procedure.

Minor anal incontinence after haemorrhoidectomy has several possible causes. Stapled haemorrhoidectomy can potentially disrupt anal function only as a result of excessive anal stretching to introduce the stapler device, but not by direct damage to the IAS during stapler firing because the mucosal purse-strings are fashioned above the level of the IAS. This is a crucial point in Longo's technique in which the minimum recommended level for the mucosal purse-string is 3–5 cm above the dentate line. This means that the staple line is above the anal canal and the IAS, not only to avoid damage to the sphincter but also to ensure efficient lifting of the prolapsed haemorrhoids. The Milligan–Morgan operation, in contrast, can injure the sphincters (mainly the IAS) either directly or sometimes after excessive anal stretching with anal retractors. However, a third mechanism may play a significant role during conventional haemorrhoidectomy: the permanent loss of sensitive anal mucosa. The present tests of anal canal sensation showed that seven of 20 patients with third-degree haemorrhoids had diminished sensitivity of the prolapsed mucosa even without any major impairment of continence. When the mucosa is repositioned and fixed in the anal canal it recovers its ability to discriminate between air and warm water. This finding compares favourably with the results of Read *et al.*[13] who found that only 54 per cent of their patients with third-degree haemorrhoids could detect the presence of water in the anal canal, while more than half of these patients had lost this ability 6 months after a Milligan–Morgan operation.

This study demonstrates that the internal and external anal sphincters are not permanently damaged by this new procedure. Sphincter morphology (width and integrity) detected by three-dimensional ultrasonography remains unchanged, function (tested by anal manometry), high-pressure zone length and RAIR also show no significant changes. Although smooth muscle fibres were found in the majority of the stapled resected specimens they belonged to the low rectum rather than to the IAS. Clinical evaluation, using two of the most widely used continence scoring systems, indicated that, after an early temporary impairment in some patients, anal continence did not change significantly in the long term. These data confirm the short-term observations by Ho *et al.*[14], although no internal sphincter injury or fragmentation was observed in the present series. This observation underlines the advantages of the new approach to the treatment of haemorrhoids: the aim is not to resect them but rather to replace them in the high anal canal, by resecting a cylinder of prolapsed mucosa above them and thus re-establishing the topographical relationship between the anal cushions and the rectal muscle layer above the high-pressure zone.

Acknowledgements

The authors thank M. V. Pragnell for revising the manuscript, and A. Veglia and M. Petrolino for active participation in the study.

References

1 Longo A. Treatment of haemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with circular suturing device: a new procedure. *6th World Congress of Endoscopic Surgery*, Rome. 1998.

2 Capomagi A, Mannetta V, Balestrieri A, Cingolani FR, Cardelli M, Proietti M *et al.* Circular hemorrhoidectomy using a stapler: the 'gold standard' for the treatment of hemorrhoids? Preliminary data regarding 206 consecutive patients. *Ital J Coloproctol* 1999; **2:** 39–43.

3 Altomare DF, Rinaldi M, Chiumarulo C, Palasciano N. Treatment of external anorectal mucosal prolapse with circular stapler: an easy and effective new surgical technique. *Dis Colon Rectum* 1999; **42**: 1102–5.

4 Beattie GC, Lam JPH, Loudon MA. A prospective evaluation of the introduction of circumferential stapled anoplasty in the management of haemorrhoids and mucosal prolapse. *Colorectal Dis* 2000; **2**: 137–42.

5 Rowsell M, Bello M, Hemingway DM. Circumferential mucosectomy (stapled haemorrhoidectomy) *versus* conventional haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355**: 779–81.

6 Mehigan BJ, Monson JR, Hartley JE. Stapling procedure for haemorrhoids *versus* Milligan–Morgan haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355**: 782–5.

7 Ho Y-H, Cheong W-K, Tsang C, Ho J, Eu K-W, Tang C-L *et al.* Stapled hemorrhoidectomy – cost and effectiveness. Randomized, controlled trial including incontinence scoring, anorectal manometry, and endoanal ultrasound assessments at up to three months. *Dis Colon Rectum* 2000; **43**: 1666–75.

8 Ganio E, Altomare DF, Gabrielli F, Milito G, Canuti S. Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy. *Br J Surg* 2001; **88**: 669–74.

9 Fazio VW. Early promise of stapling technique for haemorrhoidectomy. *Lancet* 2000; **355**: 768–9.

10 Martinelli E, Rinaldi M, Mitolo IC, Altomare DF. Computerized analysis of the rectoanal inhibitory reflex in impaired rectal function. *Techniques in Coloproctology* 1997; **1**: 64–7.

11 American Medical Systems. *Fecal Incontinence Scoring System*. Minnetonka, Minnesota: American Medical Systems, 1996.

12 Jorge JMN, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; **36**: 77–97.

13 Read MG, Read NW, Haynes WG, Donnelly TC, Johnson AG. A prospective study of the effect of haemorrhoidectomy on sphincter function and faecal continence. *Br J Surg* 1982; **69**: 396–8.

14 Ho Y-H, Tsang C, Tang CL, Nyam D, Eu K-W, Seow-Choen F. Anal sphincter injuries from stapling instruments introduced transanally: randomized, controlled study with endoanal ultrasound and anorectal manometry. *Dis Colon Rectum* 2000; **43**: 169–73.

15 Ho Y-H, Tan M. Ambulatory anorectal manometric findings in patients before and after haemorrhoidectomy. *Int J Colorectal Dis* 1997; **12**: 296–7.

Original article

Ileoanal pouch function is related to postprandial pouch tone

J. Steens, W. A. Bemelman*, W. J. H. J. Meijerink†, G. Griffioen, R. A. van Hogezand and A. A. M. Masclee

Department of Gastroenterology–Hepatology, Leiden University Medical Center, Leiden, *Department of Surgery, Academic Medical Center, Amsterdam and †Department of Surgery, Leeuwarden Medical Center, Leeuwarden, The Netherlands
Correspondence to: Dr A. A. M. Masclee, Leiden University Medical Center, C-4-P, Department of Gastroenterology and Hepatology, PO Box 9600, 2300 RC Leiden, The Netherlands (e-mail: AAMMasclee@lumc.nl)

Background: Functional impairments are frequently observed in patients with an ileoanal pouch. Meal ingestion increases pouch tone and motility. Little is known, however, about the influence of meal-stimulated pouch characteristics on pouch function. The aim was to characterize basal and postprandial pouch motor and sensory characteristics in relation to clinical pouch function in patients with an ileoanal pouch.

Methods: Nineteen patients with an ileoanal pouch, without faecal incontinence but with either a high stool frequency ($n = 8$) or an adequate stool frequency ($n = 11$), underwent pressure distension of the pouch, by which pouch compliance and sensitivity characteristics were assessed using an electronic barostat. A set pressure procedure was performed to assess the influence of a meal on pouch tone and motility.

Results: Mean(s.d.) compliance was 10(6) and 11(4) ml/mmHg in the groups with poor and adequate pouch function respectively (P not significant). Mean(s.d.) visual analogue scale scores (0–10 cm) for urge at the highest pressure of 28 mmHg were 2·3(1·0) *versus* 2·3(2·4) cm respectively (P not significant); those for pain were 0·8(1·0) *versus* 0·5(0·7) (P not significant). Postprandially mean(s.d.) pouch volume decreased by 70(24) per cent in the group with poor pouch function and 29(25) per cent in the group with adequate pouch function ($P < 0.01$). The frequency and amplitude of phasic pouch contractions increased significantly postprandially, but no differences in motility characteristics were observed between the two groups.

Conclusion: In patients with uniform pouch design and follow-up after pouch construction, pouch compliance and sensitivity were no different between patients with normal and high stool frequency; however, postprandial pouch tone was increased significantly in patients with a high stool frequency.

Paper accepted 20 June 2001

British Journal of Surgery 2001, **88**, 1492–1497

Introduction

Proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the surgical therapy of choice for severe ulcerative colitis and polyposis coli. The procedure combines cure of the colonic disease, with elimination of the need for a permanent ileostomy by preserving the natural route of defaecation. In general the quality of life after this procedure is good[1,2]. However, up to 50 per cent of patients with an IPAA may experience functional impairment such as increased stool frequency, faecal incontinence, urgency or evacuation disorders[3]. Apart from anal sphincter dysfunction, several pouch characteristics such as pouch compliance and pouch motility (large pressure waves) have been related to functional impairment after IPAA[3–7]. However, in many cases the reason for pouch dysfunction remains unclear.

It has been suggested previously that small intestinal motility is propagated into the pouch and may influence pouch function[8,9]. Recently it has been shown that pouch tone and motility are increased after a meal[10]. Patients often report a strong urge to defaecate directly after a meal. It is not known to what extent pouch function is influenced by meal-stimulated pouch tone and motility. The electronic barostat is an ideal instrument to characterize in detail not only compliance and sensory pouch characteristics but also postprandial changes in ileoanal pouch tone and motility. These characteristics of the pouch were evaluated in patients with an IPAA in relation to clinical pouch function.

Table 1 Patient characteristics

	Adequate function ($n = 11$)	Poor function ($n = 8$)	P
Age (years)*	42 (26–67)	39 (28–60)	0·66
Sex ratio (M : F)	5 : 6	3 : 5	0·73
Diagnosis			0·74
Ulcerative colitis	9	7	
Polyposis coli	2	1	
Follow-up (years)*	2·0 (0·5–5·9)	2·4 (0·5–6·0)	0·72
Day-time stool frequency*	4·6 (3–6)	7·5 (6–12)	0·01
Stool frequency at night*	0·5 (0–1)	1·9 (1–3)	0·02
Stool frequency per 24 h*	5·1 (3–7)	9·4 (8–15)	< 0·01
Urgency (min)*†	43 (15–30)	31 (2–60)	0·32
Fully continent	11	8	–
Impaired evacuation	0	0	–
Use of loperamide	1	1	–
24-h stool volume (ml)*	912 (400–1750)	973 (550–1500)	0·81

*Values are mean (range). †Time that patient was able to postpone defaecation when feeling urge

Patients and methods

In the Leiden University Medical Center each year ten to 15 patients undergo proctocolectomy with construction of an ileoanal pouch. Pouch function was evaluated using an electronic barostat in a series of patients, operated between 1994 and 1998. Patients were selected on uniformity of surgical technique and clinical pouch function. All patients had a double-stapled J pouch, which means that both the pouch and the anal anastomosis were stapled. All pouches were constructed with approximately 25 cm length of ileum. Mucosectomy was not performed. Patients who had suffered from anastomotic dehiscence, pelvic sepsis or pouchitis were excluded. Actual functional status was assessed by a detailed questionnaire that covers all gastrointestinal symptoms. Criteria for pouch function were adapted from previous reports by Oresland *et al.*[6,7]. Patients who suffered from faecal incontinence (daytime or night-time) were excluded because incontinence is mainly determined by sphincter function. It has been shown that pouch function improves during the first year after operation, but the improvement during the following 6 months is negligible[7]. Therefore follow-up was at least 6 months after construction of the pouch. In all but four patients the pouch was constructed without a diverting ileostomy. These patients were studied at least 6 months after ileostomy closure.

A total of 19 patients agreed to participate in the study. According to stool frequency, patients were divided in two groups. Patients with adequate pouch function ($n = 11$) all had a stool frequency of six or less during the day; their night-time stool frequency was once or less. Patients with poor pouch function ($n = 8$) produced more than six stools during the day and/or more than one during the night. There was no overlap in 24-h stool frequency between the two groups. Patient characteristics are presented in *Table 1*.

Barostat

An electronic barostat (Synetics Visceral Stimulator; Synetics Medical, Stockholm, Sweden) was used to distend the ileoanal pouch. A polyethylene bag (950 ml maximum capacity) was tied to the end of a 19-Fr multilumen tube. This catheter was connected to the barostat. The barostat is able to induce distensions at previously programmed constant pressures (isobaric distension). Pressure is kept constant by electronic feedback regulation of the air volume within the bag (maximal airflow 38 ml/s)[11].

Experiments started at 13.00 hours. In the morning the patients ate a light standardized breakfast and fasted thereafter. Patients were asked to stop their medication 3 days beforehand. After arrival at the department a water enema was administered to void the pouch. After calibrating the barostat, the catheter with bag was introduced through the anus and positioned 2 cm above the high-pressure zone of the anal sphincter. The subjects were lying supine in a 10° Trendelenburg position to overcome the gravitational effects of the abdominal organs. A distension procedure and a barostat procedure were performed.

Distension procedure

The bag was distended in 1-mmHg steps every 60 s to a maximum of 30 mmHg. Pressure and volume were monitored constantly and for each patient a pressure–volume curve was generated. During this procedure the operating pressure and pouch compliance was established. Operating pressure was defined as the pressure at which a volume of 80 ml was reached. Pouch compliance was defined as the maximally volume reached divided by maximal pressure.

During the experiment, perception of the urge to defaecate and abdominal pain were quantified on 100-mm visual analogue scales (VAS) in response to the questions 'How strong is your urge to defaecate?' (with endpoints on the scale ranging from very weak to very strong) and 'Do you experience lower abdominal pain?' (no pain to worst pain imaginable). Perception by means of the VAS was scored at 4, 8, 12, 16, 20, 24 and 28 mmHg. Thresholds for first sensation of urge and pain were also determined. These thresholds were defined as a VAS perception score of more than 10 mm (on a 100-mm scale). The procedure was stopped if the maximal bag volume was reached or if the subject could not tolerate further distension.

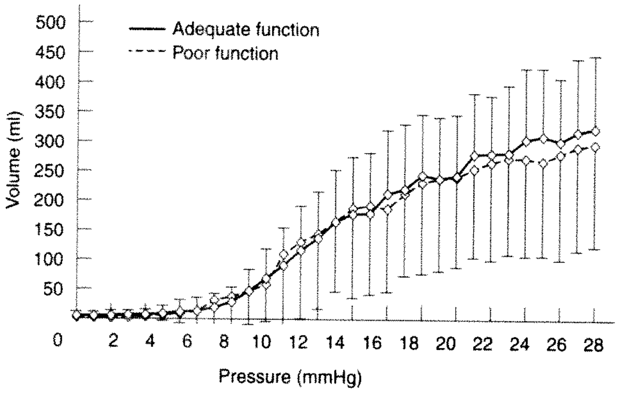


Fig. 1 Pressure–volume curve during isobaric distension (0–30 mmHg) of the ileoanal pouch in 11 patients with adequate clinical pouch function and eight patients with poor clinical pouch function. Values are mean(s.d.)

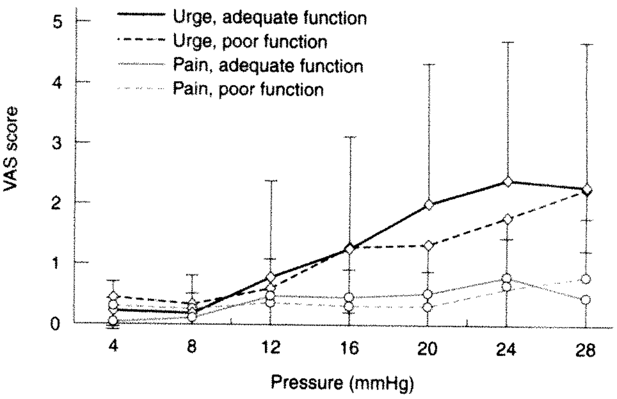


Fig. 2 Mean(s.d.) urge scores and pain scores measured on a visual analogue scale (VAS) during stepwise pressure distension of the pouch (0–30 mmHg) in eight patients with poor pouch function and 11 patients with adequate pouch function

Barostat procedure

The influence of a meal on pouch tone and motility was assessed with a barostat procedure. The bag was kept at operating pressure. Some 30 min after the start of this procedure the patients drank a semiliquid meal (580 kcal) that consisted of homogenized banana (100 g), cream (80 ml), syrup (10 ml), dextrose (10 g) and water (to 250 ml). The motor response of the pouch, in terms of pouch tone and motility, was recorded for 45 min after ingestion of the meal. Pouch tone was defined as the mean bag volume over 5-min periods before and after the meal. Pouch motility was defined as phasic reductions in pouch volume of at least 10 per cent below the baseline, lasting 10–120 s.

Statistical analysis

Unless otherwise stated, results are presented as mean(s.d.). If normal distribution could be assumed (Levine's test for equality of variances), Students' t test and two-way analysis of variance with least significant difference post-hoc testing was used. Non-parametric testing was performed with Mann–Whitney U test when appropriate. $P < 0.05$ was considered significant. Data were processed using SPSS 7.0 for Windows (SPSS, Chicago, Illinois, USA).

Results

Motor and sensory characteristics during pouch distension

In ileoanal pouches, during pouch distension with stepwise increasing pressures, the pressure–volume curve shows an S-shaped form. The pressure–volume curves of patients with adequate and poor pouch function were not significantly different (*Fig. 1*); neither was the compliance (11(4) *versus* 10(6) ml/mmHg for adequate *versus* poor function groups; $P = 0.73$). The pressure threshold for urge in the group with poor function (16(9) mmHg) was no different from that in the group with adequate function (17(5) mmHg). *Fig. 2* shows the intensity of urge and pain during pouch distension. The intensity of the urge was not significantly different between the two groups. In all patients sensation of urge was accompanied by an abdominal sensation of distension. Only two of eight patients with poor pouch function and four of 11 patients with adequate pouch function experienced pain during pressure distension. Pain sensation did not significantly increase during pressure distension.

Response to a meal

During the distension procedure and at operating pressure phasic reductions in pouch volume were observed. These contractions are called phasic volume events (PVEs). In the total group of 19 patients, the frequency of these PVEs increased from 0·48(0·29) per min before the meal to 0·70(0·27) per min postprandially ($P < 0.005$). The mean PVE amplitude also increased from 24(14) to 38(28) per cent volume reduction postprandially ($P < 0.05$). Basal and postprandial PVE characteristics (frequency, amplitude and duration) were not significantly different between patients with adequate and poor pouch function (*Table 2*). An example of phasic motility in the ileoanal pouch before and after a meal is presented in *Fig. 3*.

Table 2 Motor characteristics of the pouch registered at operating pressure in patients with adequate and poor pouch function

Phasic volume events	Adequate function (n = 11)	Poor function (n = 8)
Basal frequency (per min)	0·47(0·29)	0·50(0·32)
Postprandial frequency (per min)	0·71(0·26)	0·68(0·32)
Basal amplitude (%)	24(14)	25(16)
Postprandial amplitude (%)	33(20)	44(39)
Basal duration (s)	29(8)	30(14)
Postprandial duration (s)	33(11)	36(24)

Values are mean(s.d.). There were no significant differences between the groups

In both groups the pouch volume decreased significantly postprandially ($P < 0{\cdot}01$). However, the volume response to a meal was significantly larger in patients with poor pouch function. After 45 min, the reduction in pouch volume amounted to 70(24) per cent in patients with poor function and 29(25) per cent in patients with adequate function ($P < 0{\cdot}01$) (*Fig. 4*). The postprandial reduction in pouch volume correlated significantly with the daytime stool frequency ($r = 0{\cdot}53$, $P < 0{\cdot}05$), but not with stool volume.

Discussion

Many studies have been performed that related ileoanal pouch sensory and motor characteristics to clinical pouch function[3–7]. However, the causes of pouch dysfunction remain unclear. Pouch compliance is generally considered the most important determinant of stool frequency. However, Oresland *et al.*[7] demonstrated that it accounts for only 21 per cent of the variance in overall pouch function in a large group of patients. Pouch compliance may be affected by pouch design[12,13], period of follow-up[7], and postoperative complications such as pelvic sepsis or anastomotic dehiscence. In the present study, these factors were not significantly different between patients with adequate and poor pouch function, and there was no difference in pouch compliance between the two groups. As compliance is generally measured as the change in volume with a change in pressure up to the 'maximal tolerable volume', a component of visceral perception is implied. Therefore attention was also given to pouch sensitivity[5,6]. Pressure-driven measurement of visceroperception as performed in this study is frequently used in irritable bowel syndrome research[14–16]. It provides information not only on sensory thresholds but also on the intensity of sensations. It also provides the opportunity to study visceroperception independently of compliance. No relation between pouch sensitivity and pouch function was observed.

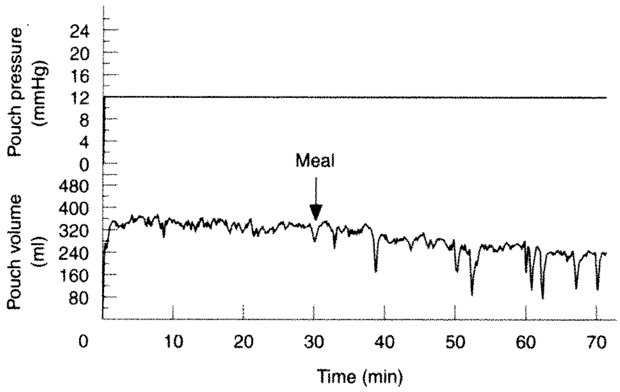


Fig. 3 Phasic volume events during a barostat procedure at operating pressure. The upper curve shows pouch pressure and the lower curve pouch volume. Postprandially, pouch volume decreased by 30 per cent in this patient. The frequency of phasic volume events increased by 41 per cent. The mean amplitude did not change after meal ingestion

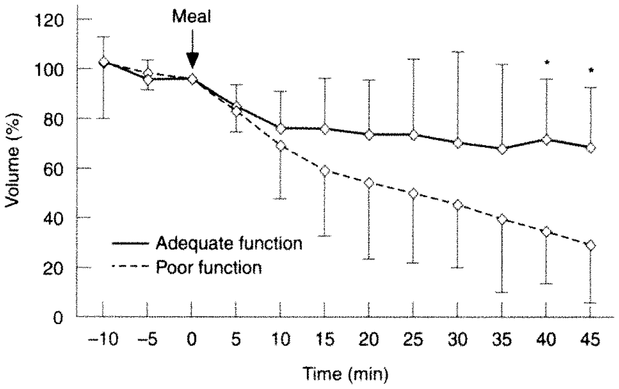


Fig. 4 Mean(s.d.) pouch volume after meal ingestion expressed as a percentage of the preprandial pouch volume during a barostat procedure at operating pressure in eight patients with poor pouch function and 11 patients with adequate pouch function. *$P < 0{\cdot}05$ *versus* poor pouch function (ANOVA)

Since many patients report urge to defaecate directly after a meal, it was assumed that it would be relevant to study pouch function after a meal. The present results confirm recent findings by Mularczyk *et al.*[10], who reported that pouch tone is increased after a meal. In addition, it was found that the increase in pouch tone is related to pouch function: the postprandial increase in pouch tone was larger in patients with poor pouch function than in patients with adequate pouch function. These results indicate that, in the absence of differences in pouch compliance, sensitivity and 24-h stool output, the postprandial meal response may have an important influence on pouch function. This may be explained as follows. The result of an increase in pouch tone is dependent on the state of filling of the pouch. If the pouch is full, the increase in tone will increase pouch pressure, resulting in urgency. If the pouch is empty, the increase in tone will reduce the pouch volume. Therefore, it will be full earlier, and the stool frequency is increased. Increased faecal volume in the pouch was unlikely because 24-h stool output was similar in the two groups. Future studies incorporating pouch scintigraphy are needed to assess to what extent the postprandial decrease in barostat volume may be due to pouch filling with small bowel content. However, Goldberg *et al.*[17] have already shown that gastrointestinal transit time does not significantly affect pouch function. A significant correlation was found between postprandial pouch tone and pouch function, but not between pouch compliance and pouch function. This implies that in patients with an IPAA the clinical significance of postprandial pouch tone is larger than that of pouch compliance. A recent report, describing two cases of ileoanal J-pouch rupture after rapid consumption of high-calorie high-fibre meals, supports this hypothesis and demonstrates that the meal response may even lead to serious complications in patients with an IPAA[18]. In the colon the tone response to a meal is well established as the gastrocolonic reflex[19,20]. The postprandial volume decrease observed in the present study in the total group of patients with an IPAA (46(32) per cent) is comparable to that observed in the colon (53(18) per cent[18]). The response is, however, much faster in the pouch than in the colon. A volume decrease of at least 10 per cent is reached in less than 10 min in the pouch, but in the colon the latency is around 45 min[19].

Phasic contractions of the ileoanal pouch have been described previously, during pressure distension as well as during continuous registration of pouch pressure. They have been associated with night-time incontinence, in patients with impaired sphincter function[4]. The present results demonstrate that PVEs are also common in patients who are continent, both during pressure distension and during continuous volume registration. Since Pescatori[9] showed that small intestinal myoelectric activity is propagated over the pouch, it might well be that PVEs in pouches are in fact representative of small intestinal motility. The present results strengthen this hypothesis as the frequency and amplitude of PVEs increased after meal ingestion. Basal and postprandial PVE characteristics (frequency, amplitude and duration) were not significantly different between patients with poor and adequate pouch function. These phasic contractions, superimposed upon reduced pouch volume and increased tone, may result in a greater urge to defaecate. Thus, pouch motility may contribute to pouch function not only in patients with incontinence and poor anal sphincter function.

In conclusion, in patients with uniform pouch design and follow-up after pouch construction, pouch compliance and sensitivity are no different between patients with normal and high stool frequency, but postprandial pouch tone is significantly increased in the latter patients. This finding suggests that medical therapy designed to reduce the magnitude of the meal effect may be an avenue worth exploring in order to improve function in patients with a high stool frequency.

References

1. McLeod RS, Baxter NN. Quality of life of patients with inflammatory bowel disease after surgery. *World J Surg* 1998; **22:** 375–81.
2. Pemberton JH, Kelly KA, Beart RWJ, Dozois RR, Wolff BG, Ilstrup DM *et al.* Ileal pouch–anal anastomosis for chronic ulcerative colitis. Long-term results. *Ann Surg* 1987; **206:** 504–13.
3. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW *et al.* Ileal pouch–anal anastomoses complications and function in 1005 patients. *Ann Surg* 1995; **222:** 120–7.
4. Ferrara A, Pemberton JH, Grotz RL, Hanson RB. Motor determinants of incontinence after ileal pouch–anal anastomosis. *Br J Surg* 1994; **81:** 285–8.
5. O'Connell PR, Pemberton JH, Brown ML, Kelly KA. Determinants of stool frequency after ileal pouch–anal anastomosis. *Am J Surg* 1987; **153:** 157–64.
6. Oresland T, Fasth S, Akervall S, Nordgren S, Hulten L. Manovolumetric and sensory characteristics of the ileoanal J pouch compared with healthy rectum. *Br J Surg* 1990; **77:** 803–6.
7. Oresland T, Fasth S, Nordgren S, Akervall S, Hulten L. Pouch size: the important functional determinant after restorative proctocolectomy. *Br J Surg* 1990; **77:** 265–9.
8. Groom JS, Kamm MA, Nicholls RJ. Relationship of small bowel motility to ileoanal reservoir function. *Gut* 1994; **35:** 523–9.
9. Pescatori M. Myoelectric and motor activity of the terminal ileum after pelvic pouch for ulcerative colitis. *Dis Colon Rectum* 1985; **28:** 246–53.
10. Mularczyk A, Contessini-Avesani E, Cesana B, Bianchi PA, Basilisco G. Local regulation of postprandial motor responses in ileal pouches. *Gut* 1999; **45:** 575–80.
11. Whitehead WE, Delvaux M. Standardization of barostat procedures for testing smooth muscle tone and sensory thresholds in the gastrointestinal tract. The Working Team of Glaxo–Wellcome Research, UK. *Dig Dis Sci* 1997; **42:** 223–41.
12. Thayer ML, Madoff RD, Jacobs DM, Bubrick MP. Comparative intrinsic and extrinsic compliance characteristics of S, J, and W ileoanal pouches. *Dis Colon Rectum* 1991; **34:** 404–8.

13 Tuckson WB, Fazio VW. Functional comparison between double and triple ileal loop pouches. *Dis Colon Rectum* 1991; **34:** 17–21.

14 Bernstein CN, Niazi N, Robert M, Mertz H, Kodner A, Munakata J *et al* Rectal afferent function in patients with inflammatory and functional intestinal disorders. *Pain* 1996; **66:** 151–61

15 Lembo T, Munakata J, Mertz H, Niazi N, Kodner A, Nikas V *et al.* Evidence for the hypersensitivity of lumbar splanchnic afferents in irritable bowel syndrome. *Gastroenterology* 1994; **107:** 1686–96.

16 Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 1995; **109:** 40–52.

17 Goldberg PA, Kamm MA, Nicholls RJ, Morris G, Britton KE. Contribution of gastrointestinal transit and pouch characteristics in determining pouch function. *Gut* 1997; **40:** 790–3.

18 Shapiro M, Hark L, Rombeau JL. Proposed association between ileoanal J-pouch perforation and rapid consumption of a high-calorie, high-fiber meal: report of two cases. *Dis Colon Rectum* 2000; **43:** 1008–11.

19 Bjornsson ES, Chey WD, Ladabaum U, Woods ML, Hooper FG, Owyang C *et al.* Differential 5-HT$_3$ mediation of human gastrocolonic response and colonic peristaltic reflex. *Am J Physiol* 1998; **275:** G498–505.

20 Cannon WB. The movements of the intestine studied by means of Röntgen rays. *Am J Physiol* 1902; **6:** 251–77.

Original article

Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative

L. Basse, J. L. Madsen and H. Kehlet

Department of Surgical Gastroenterology 435 and Department of Clinical Physiology and Nuclear Medicine 239, Copenhagen University Hospital, Hvidovre, Denmark
Correspondence to: Dr L. Basse, Department of Surgical Gastroenterology 435, Copenhagen University Hospital, Hvidovre, DK-2650 Hvidovre, Denmark (e-mail: l.basse@dadlnet.dk)

Background: Postoperative ileus usually lasts for 2–5 days after colonic surgery and may contribute to discomfort and pulmonary complications. With multimodal rehabilitation (epidural analgesia, early oral nutrition and mobilization, and laxative) defaecation occurs 1–2 days after colonic surgery. The aim of this study was to assess the transit rate of the entire gastrointestinal tract after colonic resection with multimodal rehabilitation.

Methods: Gastrointestinal motility was assessed by means of a scintigraphic method in 12 patients undergoing open colonic resection with multimodal rehabilitation and in 12 matched healthy volunteers. After intragastric or oral administration of 4 MBq ^{111}In-labelled diethylenetriamine penta-acetic acid, images of the abdomen were taken at 24 and 48 h with a double-headed γ camera.

Results: Patient and volunteer demographics were similar. The first defaecation occurred a median of 1 day after operation in the patients. Some 57 per cent of the tracer was excreted in faeces of patients and 53 per cent in faeces of volunteers ($P > 0.05$) within 48 h, indicating rapid recovery of the entire gastrointestinal motility after colonic resection with multimodal rehabilitation.

Conclusion: This study documents early normalization of the entire gastrointestinal motility assessed by an ^{111}In scintigraphic method in patients undergoing open colonic resection with a multimodal rehabilitation programme.

Paper accepted 2 July 2001

British Journal of Surgery 2001, **88**, 1498–1500

Introduction

Colonic surgery is usually followed by postoperative paralysis for 2–5 days[1]. As postoperative paralysis serves no useful purpose and may contribute to abdominal distension, discomfort and pulmonary complications, methods to improve early normalization of postoperative gastrointestinal function are warranted.

Previous work has shown that defaecation occurs 1–2 days after colonic resection with continuous epidural analgesia, enforced oral nutrition and mobilization, cisapride and laxative[2]. The duration of paralysis was assessed by the time to first defaecation, and the question remains whether multimodal rehabilitation improves the entire gastrointestinal transit or whether the effect reflects only distal rectosigmoid emptying.

The aim of this study was to assess the transit rate of the entire gastrointestinal tract using a scintigraphic method after colonic surgery with multimodal rehabilitation, and to compare the rate with that in matched unoperated controls.

Patients and methods

Twelve consecutive patients undergoing open colonic resection with a multimodal rehabilitation programme[2], including continuous epidural analgesia for 48 h with infusion of 0·25 per cent bupivacaine with morphine (0·05 mg/ml) 4 ml/h, no nasogastric tube, early postoperative oral nutrition and mobilization, oral cisapride 20 mg and magnesia 1 g every 12 h, were compared with 12 normal matched volunteers. The volunteers had a normal defaecation pattern and did not receive any medication that might modify bowel motility.

Gastrointestinal transit was assessed by means of a γ camera technique[3]. A liquid tracer comprising 4 MBq ^{111}In-labelled diethylenetriamine penta-acetic acid (DTPA) was injected into the stomach via a nasogastric tube at the end of the surgical procedure. The volunteers swallowed the tracer with 100 ml water, after which images of the abdomen were taken. Further abdominal images o both patients and volunteers were taken after 24 and 48 h

All images were obtained with subjects in supine position by means of a double-headed γ camera equipped with medium-energy general-purpose collimators and interfaced with a dedicated computer (Maxxus, Star 4000i; GE Medical Systems, Milwaukee, Wisconsin, USA). Furthermore, radioactivity in pooled vomit and pooled stools from the patients for each 24-h period was measured with the γ camera. All acquisitions lasted for 4 min.

The following regions of interest were used for integration of radioactivity on abdominal images: stomach, small intestine, ascending and transverse colon, descending colon including splenic flexure, and sigmoid colon including rectum. The counts were corrected for physical decay, and the geometric means of anterior and posterior counts were used as attenuation correction[4]. Vomit and stools were placed directly on the collimator of one head of the γ camera during measurements.

For reliable comparison with counts from gastrointestinal segments, the unattenuated counts from vomit and stools ($I(0)$) were scaled down by means of the formula: $I(x) = I(0) \times e(-\mu_l \times x)$, where μ_l denotes the linear attenuation coefficient (cm^{-1}) for ^{111}In photon energy in water and x denotes half of the patient's thickness (cm) of the abdominal dimension of the anterior–posterior plane.

Finally the percentage distribution of radioactivity in vomit, abdominal regions of interest and stool was calculated from the sum of radioactivity at 24 and 48 h. For the calculation of these regional distributions in volunteers, the amount of radioactivity passed with stools was found indirectly by subtraction of total decay and attenuation-corrected abdominal counts from initial attenuation-corrected gastric counts. The geometric centre was calculated as the segment number (1, ascending and transverse colon; 2, descending colon; 3, sigmoid colon and rectum; 4, faeces) where 50 per cent of radioactivity lay on either side. Thus, the higher the segment number, the faster the colonic transit[3].

The study was approved by the local ethics committee and written informed consent was obtained beforehand.

Statistical analysis

Data are presented as median (range). The Mann–Whitney test was used to analyse statistical differences between groups. $P < 0.05$ was considered significant.

Results

Patient and volunteer demographics were similar. There were seven women and five men in each group; the median (range) age of patients was 73 (49–89) years and that of controls was 71 (49–87) years. Colonic resection consisted of seven right hemicolectomies and five sigmoid resections. Defaecation occurred in six of the patients within 24 h after operation and in the remaining six patients between 24 and 48 h. Gastrointestinal transit in the patients and volunteers is shown in *Table 1* and an example of the scintigraphic appearance in a patient is shown in *Fig. 1*. From *Table 1* it appears that gastrointestinal transit was almost identical in patients and volunteers. In seven patients, median 43 (range 1–52) per cent of the tracer was vomited within the first 24 h after operation, but not in the volunteers. No patient vomited tracer between 24 and 48 h. Excluding the early

Table 1 Distribution of ^{111}In-labelled diethylenetriamine penta-acetic acid and the geometric centre in the gastrointestinal tract of patients undergoing colonic surgery and in healthy volunteers 24 and 48 h after administration of tracer

	Percentage of ^{111}In-labelled DTPA	
	Patients (*n* = 12)	Healthy volunteers (*n* = 12)
24 h		
Vomit (*n* = 7)	43 (1–52)	0 (0–0)
Stomach	0 (0–0)	0 (0–0)
Small bowel	0 (0–54)	0 (0–0)
Ascending and transverse colon	29 (0–100)	32 (6–57)
Descending colon	18 (0–34)	8 (0–29)
Rectosigmoid	22 (0–58)	5 (1–44)
Faeces	0 (0–51)	20 (0–80)
Geometric centre	1·46 (0·48–3·19)	2·08 (1·33–3·53)
48 h		
Vomit (*n* = 0)	0 (0–0)	0 (0–0)
Stomach	0 (0–0)	0 (0–0)
Small bowel	0 (0–49)	0 (0–0)
Ascending and transverse colon	6 (0–61)	13 (0–33)
Descending colon	7 (0–33)	4 (0–49)
Rectosigmoid	16 (0–64)	11 (0–51)
Faeces	57 (0–100)	53 (7–100)
Geometric centre	2·69 (1·65–4·00)	2·88 (2·24–4·00)

Values are median (range). DTPA, diethylenetriamine penta-acetic acid

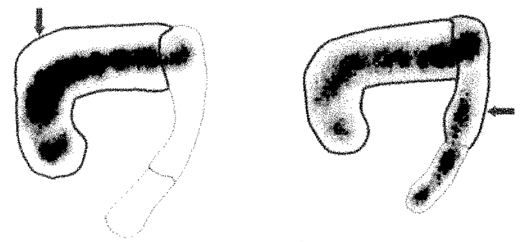

a 24h **b** 48h

Fig. 1 Scintigraphic images showing the distribution of tracer **a** 24 and **b** 48 h after sigmoid resection. Arrows indicate the position of the geometric centre of tracer

tracer vomited, 57 per cent of the tracer was excreted in faeces within 48 h in the patients and 53 per cent in the volunteers ($P > 0{\cdot}05$), indicating that gastrointestinal transit was normal with the multimodal rehabilitation regimen and that the short time to defaecation also reflected early normalization of whole gut transit. The power of the study to detect a 50 per cent difference in excretion of radioactivity between normal controls and the postoperative patients was 0·8 with a type I error of 5 per cent.

None of the patients received additional opioid analgesia during the postoperative course. Patients were discharged a median of 2 (range 2–5) days after operation, and no patient had constipation or symptoms of ileus after discharge. Two patients had complications (one wound infection, one wound dehiscence) within the first 30 days.

Discussion

This study is the first to demonstrate assessment of regional gastrointestinal transit using the ^{111}In scintigraphic method in postoperative surgical patients. The results show that a multimodal rehabilitation regimen with continuous epidural analgesia, early oral nutrition and mobilization, cisapride and laxative treatment with magnesia leads to normal gastrointestinal transit within 48 h, corresponding to the previous demonstration of a shorter time until first postoperative defaecation[2]. Although approximately half the patients vomited some tracer within the early (less than 24 h) postoperative period, this did not occur after 24 h, confirming only a short-lasting gastric paralysis[1]. These findings may have major clinical implications, as paralytic ileus may contribute to postoperative pain, discomfort and pulmonary morbidity[1].

The relative contribution of epidural analgesia, early oral nutrition, cisapride and magnesia is unknown. Several randomized trials have shown that continuous epidural analgesia reduces ileus[1], whereas the effect of early oral nutrition *per se* without epidural analgesia is debatable[1]. The effect of cisapride is probably small because a prokinetic effect has been demonstrated in only about one-half of the randomized controlled studies[1]. However, cardiac side-effects have recently been reported with cisapride, thereby preventing further use[5]. Postoperative treatment of paralytic ileus with laxatives represents an interesting concept, but has not been evaluated in randomized studies[1]. Two preliminary uncontrolled studies in patients undergoing radical hysterectomy showed early normalization of gastrointestinal function with the combined use of early nutrition and laxative treatment with oral sodium phosphate[6] or with oral magnesia and bisacolic suppositories[7]. The inhibitory effect of opioids on postoperative gastrointestinal transit is well known[1,8], and the reduced opioid regimen used in the present study[2] may have had a positive effect in this respect. Future studies must clarify the relative importance of the individual factors in reducing postoperative paralytic ileus.

In summary, these results have documented early normalization of whole gut transit in patients undergoing colonic resection with epidural analgesia, early oral nutrition and mobilization, cisapride and laxatives, as assessed by an ^{111}In scintigraphic method. These results may have important clinical implications, as early postoperative enteral nutrition may reduce catabolism and infectious complications.

Acknowledgements

This study was supported by Apotekerfonden of 1991 and the Danish Medical Research Council (grant numbers 9601607 and 9902757).

References

1 Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg* 2000; **87:** 1480–93.
2 Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232:** 51–7.
3 Graff J, Brinch K, Madsen JL. Simplified scintigraphic methods for measuring gastrointestinal transit times. *Clin Physiol* 2000; **20:** 262–6.
4 Hardy JG, Perkins AC. Validity of the geometric mean correction in the quantification of whole bowel transit. *Nucl Med Commun* 1985; **6:** 217–24.
5 Tonini M, De Ponti F, Di Nucci A, Crema F. Review article: cardiac adverse effects of gastrointestinal prokinetics. *Aliment Pharmacol Ther* 1999; **13:** 1585–91.
6 Kraus K, Fanning J. Prospective trial of early feeding and bowel stimulation after radical hysterectomy. *Am J Obstet Gynecol* 2000; **182:** 996–8.
7 Fanning J, Yu-Brekke S. Prospective trial of aggressive postoperative bowel stimulation following radical hysterectomy. *Gynecol Oncol* 1999; **73:** 412–14.
8 Cali RL, Meade PG, Swanson MS, Freeman C. Effect of morphine and incision length on bowel function after colectomy. *Dis Colon Rectum* 2000; **43:** 163–8.

Original article

Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery

C. A. Maurer, K. Z'graggen, P. Renzulli, M. K. Schilling, P. Netzer* and M. W. Büchler

Departments of Visceral and Transplantation Surgery and *Gastroenterology, Inselspital, University of Bern, CH-3010 Bern, Switzerland
Correspondence to: Professor M. W. Buchler (e-mail: markus.buechler@med.uni-heidelberg.de)

Background: The introduction of total mesorectal excision (TME) has been shown to improve local recurrence rates in rectal cancer. The present study investigated the impact of this more extensive and radical procedure with regard to autonomic pelvic nerve function.

Methods: Patients with resected primary rectal cancer were interviewed by means of a questionnaire asking about preoperative and postoperative urinary bladder and genital function. The results in patients after rectal cancer surgery without TME (group 1; $n = 29$) were compared with those obtained after introduction of the TME technique (group 2; $n = 31$). Patients in group 2 were older and had a lower level of anastomosis than patients in group 1. Other patient, treatment and tumour characteristics were comparable between the groups.

Results: Newly acquired and permanent symptoms of bladder dysfunction after rectal excision were present as follows (group 1 *versus* group 2): difficulty in bladder emptying 7 *versus* 19 per cent; sensation of incomplete bladder voiding 17 *versus* 17 per cent; urgency 17 *versus* 14 per cent; incontinence 10 *versus* 3 per cent; dysuria 7 *versus* 7 per cent; and dribbling 14 *versus* 8 per cent. Male patients stated the following sexual functions before operation/after operation in group 1 *versus* group 2: interest in sex 80 per cent/40 per cent *versus* 63 per cent/37 per cent; sexually active 67 per cent/7 per cent *versus* 53 per cent/22 per cent; impotence 75 per cent/6 per cent *versus* 58 per cent/26 per cent; ability to have intercourse 75 per cent/13 per cent *versus* 67 per cent/29 per cent; ability to achieve orgasm 88 per cent/13 per cent *versus* 76 per cent/47 per cent; and orgasm with ejaculation 88 per cent/9 per cent *versus* 76 per cent/53 per cent.

Conclusion: While both conventional rectal cancer surgery and TME result in similarly favourable postoperative bladder function, both techniques decrease sexual function. However, TME offers a significant advantage with regard to preservation of postoperative sexual function in men and constitutes a true advance in rectal cancer surgery compared with conventional techniques.

Presented in part at a postgraduate course, Bern, Switzerland, December 1998, for regional physicians, gastroenterologists and general surgeons; and to the annual meeting of the Bavarian Surgeons, Erlangen, Germany, July 1999; and published in abstract form in Thetter O, Passlick B, Bauer H, Metak G, eds. 76. Tagung der Vereinigung der Bayrischen Chirurgen Wissenschaftliche Referate. Munich: Hieronymus, 1999

Paper accepted 26 June 2001

British Journal of Surgery 2001, 88, 1501–1505

Introduction

In the Western world, colorectal cancer is the most common malignancy of the alimentary tract[1] and the rectum is the most frequently involved site, bearing about 35 per cent of all colorectal tumours[2]. Two of the main problems of rectal cancer surgery are local recurrence and pelvic autonomic nerve damage. The incidence of sexual dysfunction following conventional rectal surgery, i.e. rectal surgery without consideration of the anatomical planes of the pelvic fascia and pelvic autonomic nerves, is reported to be as high as 94 per cent[3] and the incidence of bladder dysfunction has been documented at 73 per cent[4,5]. Clearly, adequate removal of the tumour is the first priority of surgery. This goal can be achieved with total mesorectal excision (TME)[6], which is gaining in acceptance[7]. TME is characterized by a sharp dissection between the parietal and visceral planes of the pelvic fascia. The principle of this technique is *en bloc* removal of the complete rectum and mesorectum together with any potential spread of cancer into the perirectal fat, leaving negative surgical margins. Local recurrence rates of 8 per cent and less are now reported from several institutions[8,9]. In comparison to conventional rectal resection, the TME procedure is more radical and extensive, and therefore has a potentially adverse effect on pelvic autonomic nerve function. On the other hand, TME demands a more precise dissection, respecting the anatomical planes and preserving the autonomic pelvic nerves that are adjacent to the resection plane. TME was introduced as a standard technique for treatment of resectable rectal cancer in the authors' department in the second half of 1995. The aim of this study was to investigate the influence of TME on urogenital function.

Patients and methods

From November 1993 to September 1998, 133 consecutive patients underwent surgery for rectal cancer, defined as adenocarcinoma within 15 cm of the anal verge. A questionnaire regarding preoperative and current urogenital function was sent to all 87 patients who were alive in December 1998 after radical rectal cancer surgery. A minimum postoperative follow-up of 3 months was obtained for each patient. Sixty-three patients answered the questionnaire (response rate 72 per cent) and 60 questionnaires contained reliable data.

The questionnaire consisted of questions relating to difficulty in bladder emptying, sensation of incomplete bladder voiding, dribbling, urgency, leakage of urine, dysuria and frequency of micturition. The sexual function section of the questionnaire included questions concerning libido, sexual activity and orgasm in all patients; arousal, vaginal lubrication and dyspareunia in women; and ability to have erection, ejaculation and sexual intercourse in men. Except for frequency of micturition, all questions had four possible answers: never, rare, frequent or always. The first two categories were classified as absence of a specific symptom, the latter two as presence of a specific symptom. To detect subjective functional deterioration the questions comprised preoperative and postoperative urogenital function.

The conventional rectal excision consisted of a dissection of the superior rectal artery and further preparation towards the pelvis directly on the aortic bifurcation and the common iliac arteries. Posterior mobilization of the rectum was done bluntly by the surgeon's hand whereas the mesorectum was sharply dissected laterally on both sides between clamps with suture ligation. Anteriorly, either sharp or blunt dissection was used. No specific attention was paid to autonomic nerve preservation. Therefore, the superior hypogastric plexus, hypogastric nerves and the inferior hypogastric plexus were at high risk of accidental removal, tearing or suture entrapment.

The technique of TME as described by Heald *et al.*[6] involved complete removal of the mesorectum and the mesentery containing the inferior mesenteric artery and vein by meticulous sharp dissection of the avascular plane, the so-called holy plane[10], between the parietal and visceral pelvic fascia. Anteriorly, the specimen included the intact Denonvillier's fascia and the peritoneal reflection. Autonomic nerve preservation consisted of identification and sparing of the preaortic superior hypogastric plexus and the bilateral hypogastric nerves that join the sacral parasympathetic nerves (nn. erigentes) to form the inferior hypogastric plexus anterolaterally on both sides. At this point, little autonomic nerves branching off the inferior hypogastric plexus directly into the rectum required division and damage to the inferior hypogastric plexus itself was avoided. Exceptionally, locally advanced rectal tumours with adherence or infiltration necessitated sacrifice of these pelvic nerve structures to obtain a clear lateral resection margin. By the end of 1995 the surgeons' technique was considered to have improved substantially, and it was possible to obtain rectal specimens completely surrounded by intact mesorectum along the holy plane and to preserve the pelvic autonomic nerves.

The impact of TME on pelvic nerve preservation was investigated in two groups with similar patient characteristics and treated by the same team of surgeons: 29 patients in group 1 underwent conventional rectal cancer surgery from 1993 to 1995, and 31 in group 2 underwent mesorectal excision from 1996 to 1998. Within group 2, 28 patients had total mesorectal excision and three had partial mesorectal excision. Patient, treatment and tumour-related characteristics of both groups are listed in *Table 1*.

Statistical analysis

Results were expressed as mean(s.e.m.) or median (range). Differences between the two groups (conventional surgery *versus* TME) regarding age, distances of tumour and of anastomosis from anal verge, and frequency of micturition (quantitative data) were analysed with a Mann–Whitney *U* test. Differences in the remaining patient, treatment and tumour characteristics (categorical data) were calculated by the use of a χ^2 test. Postoperative urogenital functions were compared with the preoperative data as well as between groups 1 and 2 by the χ^2 test. Differences between preoperative and postoperative frequencies of micturition within the same group were examined by the use of a Wilcoxon signed rank test. Statistical significance was attributed at the 5 per cent level. The Winstat (version 5.3;

Table 1 Patient, treatment and tumour characteristics

	Conventional	TME	*P*
No. of patients	29	31	
Women	12	12	n.s.‡
Men	17	19	n.s.‡
Median age at operation (years)	63·9	71·2	< 0·01§
Median age at interview (years)	67·4	73·1	< 0·04§
Mean tumour distance from anal verge (cm)	8·5	8·5	n.s.§
Type of operation			
(Low) anterior resection	26	29	n.s.‡
Abdominoperineal resection	3	2	n.s.‡
Mean distance of anastomosis from anal verge (cm)	6·4	4·7	< 0·03§
Tumour stage*			
I (including *in situ* carcinoma)	13	14	n.s.‡
II	10	7	n.s.‡
III	4	7	n.s.‡
IV	2	3	n.s.‡
Radiation therapy†	5	4	n.s.‡
Surgical complications	4	4	n.s.‡
Local recurrence detected at follow-up	3	1	n.s.‡

*Union Internacional Contra la Cancrum classification. †Before or after operation. TME, total mesorectal excision. n.s., not significant. ‡χ^2 test. §Mann–Whitney *U* test

Table 2 Bladder function before and after operation

	Before operation			After operation			
	Conventional	TME	*P*	Conventional	TME	*P**	*P*†
Difficulty emptying bladder	0 of 29	3 of 31	n.s.	2 of 29	9 of 31	< 0·05	n.s.
Sensation of incomplete bladder voiding	1 of 29	3 of 31	n.s.	6 of 29	8 of 29	n.s.	n.s.
Urgency	3 of 29	5 of 31	n.s.	8 of 29	9 of 29	n.s.	n.s.
Leaking of urine	2 of 29	2 of 30	n.s.	5 of 29	3 of 30	n.s.	n.s.
Pain or burning during urination	1 of 29	2 of 31	n.s.	3 of 29	4 of 30	n.s.	n.s.
Dribbling at end of urination	3 of 29	6 of 31	n.s.	7 of 29	8 of 29	n.s.	n.s.

*Considering all patients; †excluding patients who already had poor function before surgery (χ^2 test). TME, total mesorectal excision. n.s., not significant

Microsoft Corporation, Redmond, Washington, USA) computerized statistical analysis system was used.

Results

Data on urinary function are summarized in *Table 2*, except for frequency of micturition. Even before rectal cancer surgery, 0–19 per cent of the patients with rectal cancer suffered often or always from one or more symptoms of urinary dysfunction. There was no significant difference in urinary symptoms between patients who had conventional rectal cancer surgery (group 1) and those who had TME (group 2), either in the preoperative occurrence of symptoms or as a consequence of the operation, other than more frequent difficulty in emptying the bladder following TME. However, this difference was not significant if patients already affected before surgery were excluded from both groups. None of the urinary symptoms was found significantly more often after than before operation, apart from a more frequent sensation of incomplete bladder voiding in group 1. Some patients even reported improved urinary function following rectal cancer resection: two patients in each group had less urgency; one patient in each group declared improvement in the sensation of incomplete bladder voiding and of discomfort during micturition; one patient in group 1 no longer suffered from incontinence; three patients in group 2 noted improved bladder voiding and two patients improved with respect to terminal dribbling.

The mean frequency of micturition per 24 h increased from 5·3(0·4) before operation to 6·7(0·4) after resection in group 1 ($P < 0.001$) and from 6·3(0·4) to 6·7(0·4) in group 2 ($P > 0.1$). The postoperative increase in frequency was significantly higher in group 1 than in group 2 ($P < 0.03$).

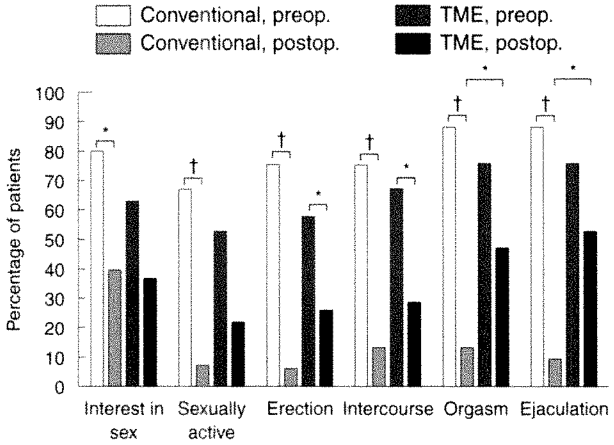


Fig. 1 Frequency of six different features of male genital function in group 1 (conventional rectal surgery) and group 2 (total mesorectal excision; TME) before and after operation. Preop., before operation; postop., after operation. $^*P < 0.05$, $^\dagger P < 0.001$ (χ^2 test)

Fig. 1 shows the preoperative and postoperative impairment of male genital function in both groups. Compared with conventional rectal cancer surgery, TME significantly preserved the ability to achieve orgasm and to ejaculate. These differences still remained significant if patients with pre-existing poor genital function were excluded from the statistical analysis. In this subgroup analysis, preserved erectile function was significantly more common in the TME group than after conventional surgery ($P < 0.05$). If preoperative sexual function was compared with the current postoperative function within each group, the functional deterioration as a consequence of conventional surgery was highly significant ($P < 0.001$ for five of six symptoms) whereas in the TME group only the ability to have erection and intercourse was significantly reduced ($P < 0.05$) (*Fig. 1*).

Of the 24 women, 14 refused to answer the detailed questions, specifically for sexual function. Their reasons for not completing this part of the questionnaire were: sexual inactivity (eight patients), shame (two) and not specified (four). The remaining ten women (four in group 1 and six in group 2) stated the following sexual functions before operation/after operation in group 1 *versus* group 2: interest in sex 33 per cent/33 per cent *versus* 43 per cent/29 per cent; sexually active 0 per cent/0 per cent *versus* 18 per cent/14 per cent; arousal 25 per cent/25 per cent *versus* 50 per cent/33 per cent; vaginal lubrication during arousal 33 per cent/33 per cent *versus* 17 per cent/0 per cent; and ability to achieve orgasm 25 per cent/25 per cent *versus* 40 per cent/50 per cent.

None of the men or women declared improvement in any of the genital functions after rectal surgery.

Discussion

Surgical performance has been shown to be one of the most important prognostic factors in patients with rectal cancer[11]. In the quest for reduced recurrence rates and improved survival after surgery for rectal cancer, excision techniques have become more radical[6,9,12]. Mesorectal excision can improve these results[9,13] but, unless meticulous attention is paid to autonomic nerve preservation, this more radical approach may theoretically result in impotence. This study investigated the influence of the TME technique on the outcome of urogenital function following rectal cancer surgery.

Regarding urinary function alone, the incidence of pelvic surgery-related impairment was rather low and not significantly different between group 1 (conventional surgery) and group 2 (TME technique). However, the level of anastomosis in group 2 was significantly lower in the pelvis than in group 1, and therefore the likelihood of damaging the delicate inferior hypogastric plexus, the sympathetic–parasympathetic control site for the urinary bladder, was higher in group 2. TME may be regarded as beneficial since this procedure, although more radical, did not increase the percentage of patients with postoperative urinary dysfunction. The higher postoperative frequency of micturition in group 1 might be an expression of incomplete bladder voiding in some patients, although the incidence of the corresponding subjective feeling was not significantly different between both groups. Surprisingly, a few patients in each group showed improvement in urinary bladder function after the operation. It might be speculated that some bulky rectal tumours can provoke bladder symptoms that vanish with removal of the tumour.

Introduction of the well defined and standardized technique of TME led to a significant reduction in sexual dysfunction in men compared with the results obtained with the conventional technique. TME reduced postoperative impotence in half and the inability to achieve orgasm in more than half compared with the conventional technique. One of the most striking findings was that, in contrast to conventional rectal cancer surgery, TME completely avoided the problem of retrograde ejaculation. Apparently, the hypogastric nerve descending on both sides from the preaortic superior hypogastric plexus is at high risk of damage during conventional blunt dissection of the rectum[14]. Furthermore, if the surgeon is not familiar with the TME technique there may be some difficulty entering the correct plane at the pelvic brim and preserving a thin layer of preaortic connective tissue that contains the superior hypogastric plexus and the hypogastric nerves.

The better results in the TME group cannot be attributed to a bias from positive patient selection, i.e. group 2 representing the more favourable patients. On the contrary, better results would be expected in group 1 because the median age was less than that of patients in group 2. Similarly, the level of anastomosis in group 2 was significantly closer to the anal verge than that in group 1. This demonstrates that a more radical resection in the correct plane preserves the autonomic pelvic nerves significantly better than conventional, partly blunt dissection. These data indicate that TME offers a significant advantage with regard to postoperative sexual function in men and constitutes real surgical progress compared with conventional techniques.

The data on postoperative sexual function in women are not conclusive, since a high percentage of the female patients were sexually inactive and indifferent to sex even before the operation. Furthermore, the number of usable questionnaires was small since 14 patients did not answer or only selectively answered questions regarding sexual function, a problem that has been encountered previously[12,13,16].

An important finding was the substantial number of patients with rectal cancer complaining of poor urogenital function before surgery. Symptoms of preoperative bladder disturbance were reported in up to 19 per cent of patients, and preoperative loss of potency was reported in 34 per cent of all male patients. Similar findings were reported by Leveckis *et al.*[5]. While surgery is responsible for some postoperative urogenitory disorders, some patients blame surgery for pre-existing conditions that they have difficulty accepting. It can be argued that autonomic pelvic nerve damage may not be a major concern for patients who undergo rectal cancer resection due to senile involution because the majority are beyond the age at which they engage in regular or frequent sexual intercourse. Despite this, the surgeon should aim to preserve the anatomical structures necessary for undisturbed urogenital function. Every colorectal surgeon and most general surgeons will at some point be confronted with younger patients suffering from rectal cancer for whom a loss of potency and loss of normal sexual function would substantially reduce the quality of life. Consistently good functional results can only be achieved by the use of and training in this nerve-sparing technique.

This is the first study to investigate the effect of TME on urinary and sexual function in comparison to the results obtained by conventional rectal cancer surgery, both performed by the same team of surgeons and at the same institution. Rectal cancer surgery decreased male sexual function but introduction of the TME technique significantly increased the number of men with preserved genital function. In addition, surgically acquired bladder dysfunction was observed rather infrequently in both groups and was not enhanced by the introduction of TME.

References

1 Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997; **47**: 5–27.

2 Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD *et al.* Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; **112**: 594–642.

3 Havenga K, Maas CP, DeRuiter MC, Welvaart K, Trimbos JB. Avoiding long-term disturbance to bladder and sexual function in pelvic surgery, particularly with rectal cancer. *Semin Surg Oncol* 2000; **18**: 235–43.

4 Cunsolo A, Bragaglia RB, Manara G, Poggioli G, Gozzetti G. Urogenital dysfunction after abdominoperineal resection for carcinoma of the rectum. *Dis Colon Rectum* 1990; **33**: 918–22.

5 Leveckis J, Boucher NR, Parys BT, Reed MW, Shorthouse AJ, Anderson JB. Bladder and erectile dysfunction before and after rectal surgery for cancer. *Br J Urol* 1995; **76**: 752–6.

6 Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? *Br J Surg* 1982; **69**: 613–16.

7 Heald RJ. Total mesorectal excision is optimal surgery for rectal cancer: a Scandinavian consensus. *Br J Surg* 1995; **82**: 1297–9.

8 Maurer CA, Renzulli P, Meyer JD, Buchler MW. Rectal carcinoma. Optimizing therapy by partial or total mesorectum removal. *Zentralbl Chir* 1999; **124**: 428–35.

9 McCall JL. Total mesorectal excision: evaluating the evidence. *Aust N Z J Surg* 1997; **67**: 599–602.

10 Heald RJ. The 'Holy Plane' of rectal surgery. *J R Soc Med* 1988; **81**: 503–8.

11 Porter GA, Soskolne CL, Yakimets WW, Newman SC. Surgeon-related factors and outcome in rectal cancer. *Ann Surg* 1998; **227**: 157–67.

12 Moriya Y, Sugihara K, Akasu T, Fujita S. Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. *Eur J Cancer* 1995; **31A**: 1229–32.

13 Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998; **133**: 894–9.

14 Masui H, Ike H, Yamaguchi S, Oki S, Shimada H. Male sexual function after autonomic nerve-preserving operation for rectal cancer. *Dis Colon Rectum* 1996; **39**: 1140–5.

15 Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. *Br J Surg* 2000; **87**: 206–10.

16 Banerjee AK. Sexual dysfunction after surgery for rectal cancer. *Lancet* 1999; **353**: 1900–2.

Original article

Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging

G. L. Morren, R. G. H. Beets-Tan* and J. M. A. van Engelshoven*

Departments of General Surgery and *Radiology, University Hospital of Maastricht, Maastricht, The Netherlands
Correspondence to: Dr G. L. Morren, Rodestraat 36, B-3290 Diest, Belgium (e-mail: geert_morren@hotmail.com)

Background: The anatomy of the anal canal and perianal structures has been imaged using endoluminal magnetic resonance imaging (MRI). Phased-array MRI avoids the use of an endoluminal coil that may distort anatomy. The aim of this study was to describe the anatomy of the anal canal and perianal structures using phased-array MRI.

Methods: Imaging was performed in 14 men and 19 nulliparous women. The dimensions of the anal canal, puborectalis, external anal sphincter, perineal body, superficial transverse perineal muscle, bulbospongiosus, ischiocavernosus and anococcygeal body were measured in different planes, and sex differences were calculated.

Results: The lateral canal was significantly longer than its anterior and posterior part ($P < 0{\cdot}001$). The anterior external anal sphincter was shorter in women than in men ($P = 0{\cdot}01$) and occupied, respectively, 30 and 38 per cent of the anal canal length ($P = 0{\cdot}001$). The caudal ends of the external anal sphincter formed a double layer. The perineal body was thicker in women than in men ($P < 0{\cdot}001$) and easier to define. The superficial transverse muscles had a lateral and caudal extension to the ischiopubic bones. The bulbospongiosus was thicker in men than in women ($P < 0{\cdot}001$). The ischiocavernosus and anococcygeal body had the same dimensions in both sexes.

Conclusion: Phased-array MRI is a non-invasive technique that allows an accurate description of the normal anatomy of the anal canal and perianal structures.

Paper accepted 8 July 2001

British Journal of Surgery 2001, **88**, 1506–1512

Introduction

Over recent decades, knowledge of the anatomy of the anal canal and perianal structures has grown rapidly. New dissection techniques have revealed major differences between the sexes[1,2] and a new concept of the anal sphincter mechanism has been presented[3]. Endoanal ultrasonography made it possible to describe the normal anatomy of the anal sphincters *in vivo*[4,5], but it has some limitations. It is highly operator dependent and its limited field of view and contrast resolution make it less suitable for the study of pelvic floor muscles. Magnetic resonance imaging (MRI) with an endoanal coil allows a detailed description of both the anal canal and perianal structures in three dimensions[6–9]. However, the use of an endoanal coil also has major disadvantages. Insertion of the coil may be uncomfortable and may disturb the anal and perianal anatomy. The presence of the coil may be unpleasant or even painful, and only structures near the coil can be imaged.

Recently, phased-array MRI has been used to obtain high-resolution spatial images of the entire anorectal region without the disadvantages of endoanal MRI or ultrasonography[10].

Functional disorders of the anorectum may be caused by injury to the anal canal or perianal structures. Phased-array MRI has the potential to detect this structural damage[11] but, to do so accurately, a detailed knowledge of the normal anatomy in three dimensions is needed.

The aim of this study was to describe normal, undisturbed anatomy of the anal canal and perianal structures in both men and nulliparous women using high-resolution phased-array MRI.

Methods

Nineteen nulliparous women and 14 men with no history of anorectal disease or surgery were examined. All gave informed consent. The institutional ethics committee approved the study.

Magnetic resonance imaging

MRI was performed at 1·5 Tesla (Gyroscan, Powertrak 6000, NT release 6.2.1, 23·0 mT m^{-1}, rise time 0·2 ms, slew rate 105 T m^{-1} s^{-1}; Philips Medical Systems, Best, The Netherlands). All subjects were positioned supine with their pelvis centred on the proximal end of a quadrature phased-array spine coil in a feet-first position. Sequences used were a T1-weighted, two-dimensional, turbo spin echo (T1W TSE: TR/TE 656/10 ms, 5 echo train length, 8-mm slice thickness, 0·8-mm gap, four signal averages, 166 × 256 matrix, 25-cm field of view (FOV), 1·4-min acquisition time) and a T2-weighted, two-dimensional, turbo spin echo (T2W TSE: TR/TE 3427/150 ms, 25 echo train length, 3-mm slice thickness, 0·3-mm gap, eight signal averages, 175 × 256 matrix, 20-cm FOV, 2·64-mm^3 voxel size, 6·5-min acquisition time). T2W sequences were obtained in sagittal, coronal and axial planes. The T1W TSE sequence was obtained in the axial plane and served for accurate planning of the coronal and axial T2W sequences as it was important to angle these planes exactly parallel and perpendicular to the long axis of the anal canal. Patients did not receive bowel preparation and no catheters were inserted in the anal canal during the procedure. The total scan time of the phased-array MRI was 20 min.

Image review and measurements

Images were stored on an optical disk and reviewed at an Easy Vision Workstation (Philips Medical Systems). The internal anal sphincter was slightly isointense to hyperintense relative to striated muscle tissue. Fat tissue was hyperintense. Measurements were performed using software callipers on a 0·01-mm scale. Values were expressed in millimetres. Measurements of 'length' were made along the craniocaudal axis in the sagittal or coronal plane, measurements of 'thickness' along the anteroposterior axis in the axial or sagittal plane, and measurements of 'width' along the lateral axis in the coronal plane. Within a chosen plane, each structure was measured at its largest dimension. Bilateral structures were measured on the left side. Anal canal length was measured from the most cranial border of the puborectalis to the most caudal border of the external anal sphincter (EAS). Only terms listed in *Terminologia Anatomica*[12] were used.

Statistical analysis

Values are given as median (range). Ninety-five per cent confidence intervals (c.i.) for the difference between medians were calculated. The Mann–Whitney *U* test was used for comparisons between sexes and the Kruskal–Wallis test for comparisons between anterior, lateral and posterior components of the anal canal. $P \leq 0{\cdot}05$ was considered significant.

Results

The male and female groups had a similar age distribution with a median (range) age of 27 (19–57) and 32 (19–68) years respectively.

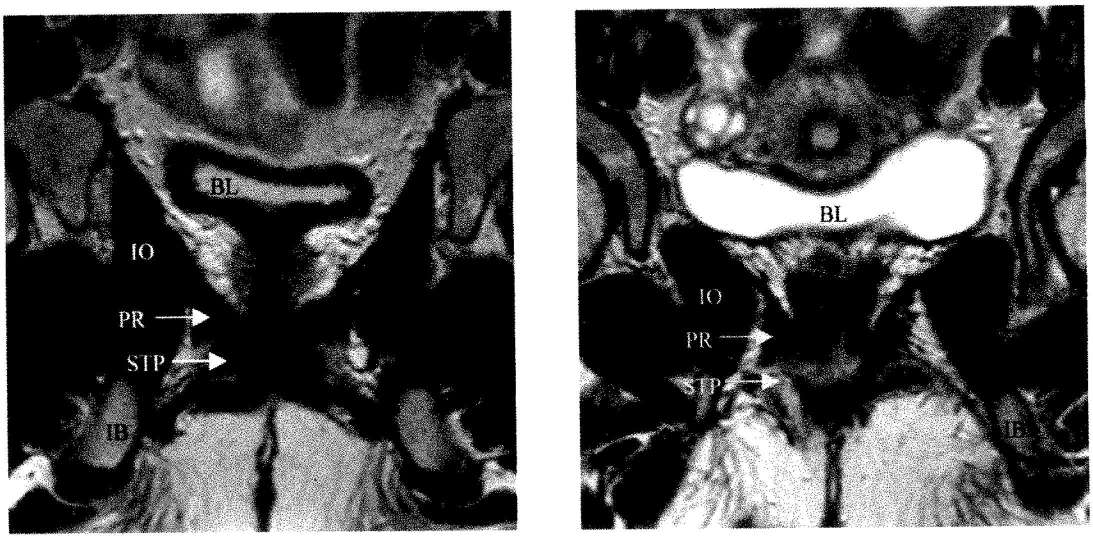
Length of anal canal components

Results are given in *Table 1*. The length of the lateral anal canal was significantly greater than that of its anterior and posterior parts. Women had a longer lateral anal canal than men. The anterolateral part of the puborectalis was significantly longer than its lateral and posterior parts. The lateral part of the EAS was significantly longer than its anterior and posterior part. In women, the EAS was shorter anteriorly and longer posteriorly than in men. The anterior EAS occupied 30 per cent of the anal canal in women and 38 per cent in men (95 per cent c.i. – 15 to – 4; $P = 0{\cdot}001$). The posterior part of the puborectalis occupied 31 per cent of the anal canal in women and 33 per cent in men (95 per cent c.i. – 11 to 0; *P* not significant).

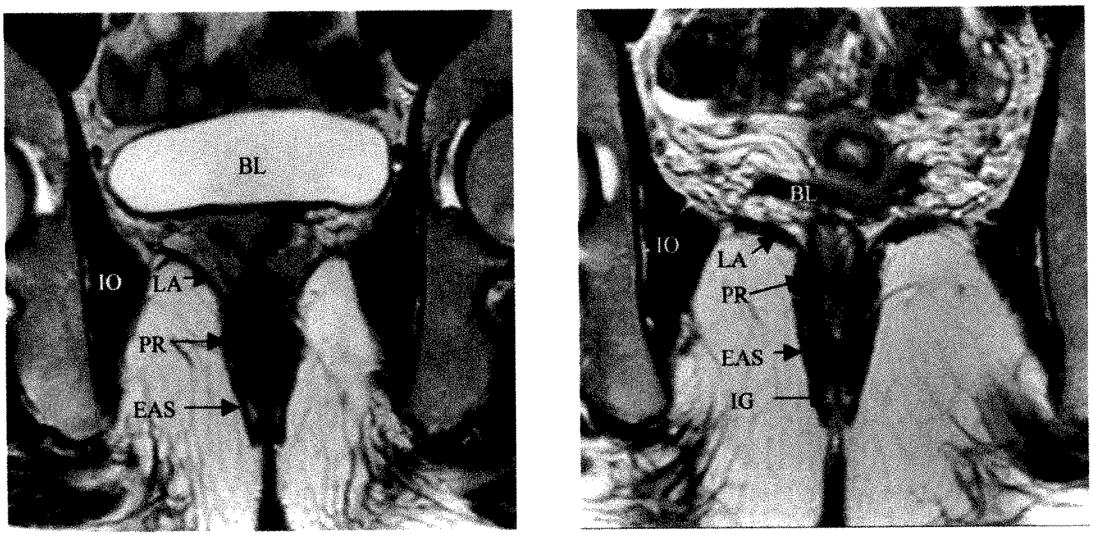
Table 1 Sex differences in the length of anal canal components

	Median (range) length (mm)			
	Women ($n = 19$)	Men ($n = 14$)	95 per cent c.i.	*P**
Anal canal				
Anterior	38 (24–57)	37 (32–48)	– 6 to 4	n.s.
Lateral	49 (36–58)	41 (38–48)	3 to 10	0·004
Posterior	38 (27–49)	34 (24–43)	– 1 to 6	n.s.
P†	< 0·001	< 0·001		
Puborectalis				
Anterolateral	24 (14–30)	22 (15–29)	– 2 to 5	n.s.
Lateral	16 (9–24)	15 (9–23)	– 4 to 0	n.s.
Posterior	12 (5–15)	11 (8–19)	– 3 to 1	n.s.
P†	< 0·001	< 0·001		
External anal sphincter				
Anterior	11 (8–15)	14 (9–19)	– 5 to – 1	0·01
Lateral	29 (20–39)	26 (17–36)	– 3 to 8	n.s.
Posterior	16 (10–23)	14 (7–15)	0 to 5	0·02
P†	< 0·001	< 0·001		

c.i., Confidence interval of median differences between sexes; n.s. not significant. *Mann–Whitney *U* test for comparisons between sexes; †Kruskal–Wallis test for comparisons between anterior, lateral and posterior components of the anal canal



a Male **b** Female



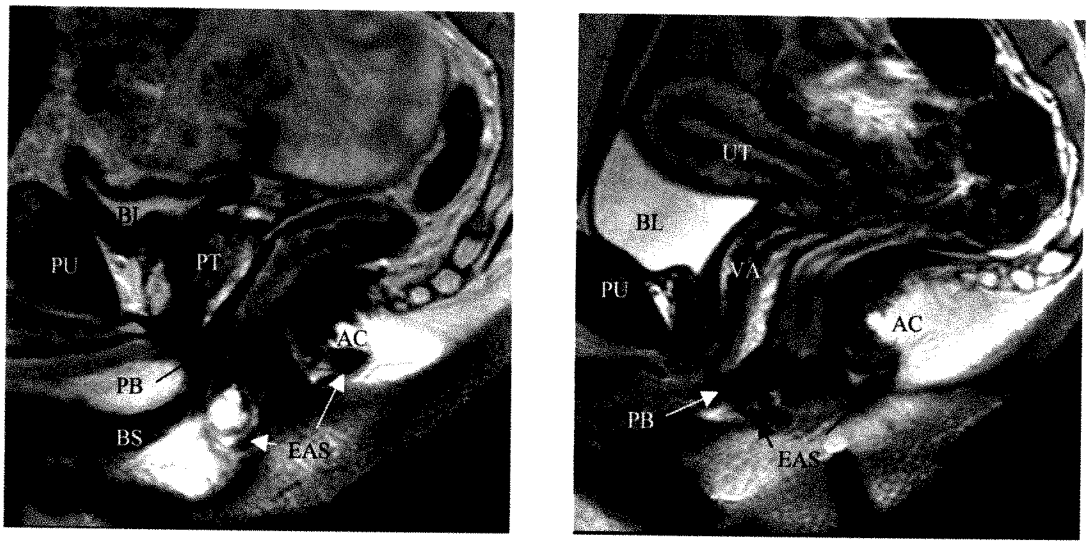
c Male **d** Female

Fig. 1 Coronal phased-array magnetic resonance images of the anal canal and perianal structures; **a** male and **b** female anatomy anterior to the anal canal, **c** male and **d** female anatomy through the mid-anal canal. BL, bladder; EAS, external anal sphincter; IO, internal obturator muscle; IG, intersphincteric groove; IB, ischiopubic bone; LA, levator ani; PR, puborectal muscle; STP, superficial transverse perineal muscle

Configuration of the anal canal

The EAS appeared as the outermost hypointense layer surrounding the lower part of the anal canal. In the coronal plane, the caudal ends of the EAS folded inwards and upwards, forming a double layer (*Fig. 1c,d*). The length of the inner layer of the EAS was 7 (5–13) mm in men and 7 (5–11) mm in women. The inner layer was separated from the internal anal sphincter by the intersphincteric groove, which measured 2·5 (2–7) mm in men and 3 (2–5) mm in women. In the sagittal plane, caudal fibres from the outer layer of the EAS extended anteriorly and posteriorly to connect with the bulbocavernosus and anococcygeal body. Fibres from both the inner and outer layer bent upwards, forming the anterior EAS (*Fig. 2a,b*). There was no difference between the thickness of the anterior EAS in men (3 (2–7) mm) and women (3·5 (2–7) mm).

The puborectalis surrounded the upper lateral and posterior parts of the anal canal. Anterolaterally, the puborectalis became longer and wider, forming the pubo-



a Male

b Female

Fig. 2 Sagittal phased-array magnetic resonance images of the anal canal and perianal structures; **a** male and **b** female anatomy in the mid-sagittal plane. AC, anococcygeal body; BL, bladder; BS, bulbospongiosus; EAS, external anal sphincter; PB, perineal body; PT, prostate; PU, pubic bone; UT, uterus; VA, vagina

perinealis (*Fig. 3c,d*). The distance between the left and right puboperinealis measured 18 (10–24) mm in men and 15 (11–21) mm in women. In 30 per cent of the subjects, the puborectalis overlapped the EAS for a distance of between 2 and 5 mm in the mid-coronal plane. In the axial plane, the anteroposterior axis of the anal canal was longer than the lateral axis (*Fig. 3*).

Dimensions of perianal structures

The dimensions of different perianal structures are given in *Table 2*. The perineal body in women was clearly visible as a separate anatomical structure located between the posterior vaginal wall and the anterior anal canal (*Fig. 2b*). In men, the perineal body was smaller and more difficult to define (*Fig. 2a*). In the axial plane, the male perineal body appeared as a central point connecting the different perineal muscles (*Fig. 3a*).

In the axial plane, the superficial transverse perineal muscle was most often seen as a wide and thin muscular layer cranial to the anterior EAS and connected to the perineal body (*Fig. 3a,b*). In the coronal plane, the left and right superficial transverse perineal muscles were separated medially by the posterior and caudal parts of the bulbospongiosus muscles. They inserted laterally into the fascia of the ischiocaverous muscles and the periosteum of the ischiopubic bone (*Fig. 1a,b*).

Both the ischiocavernosus and bulbospongiosus were clearly visible (*Fig. 3b,c*). The latter was thicker in men.

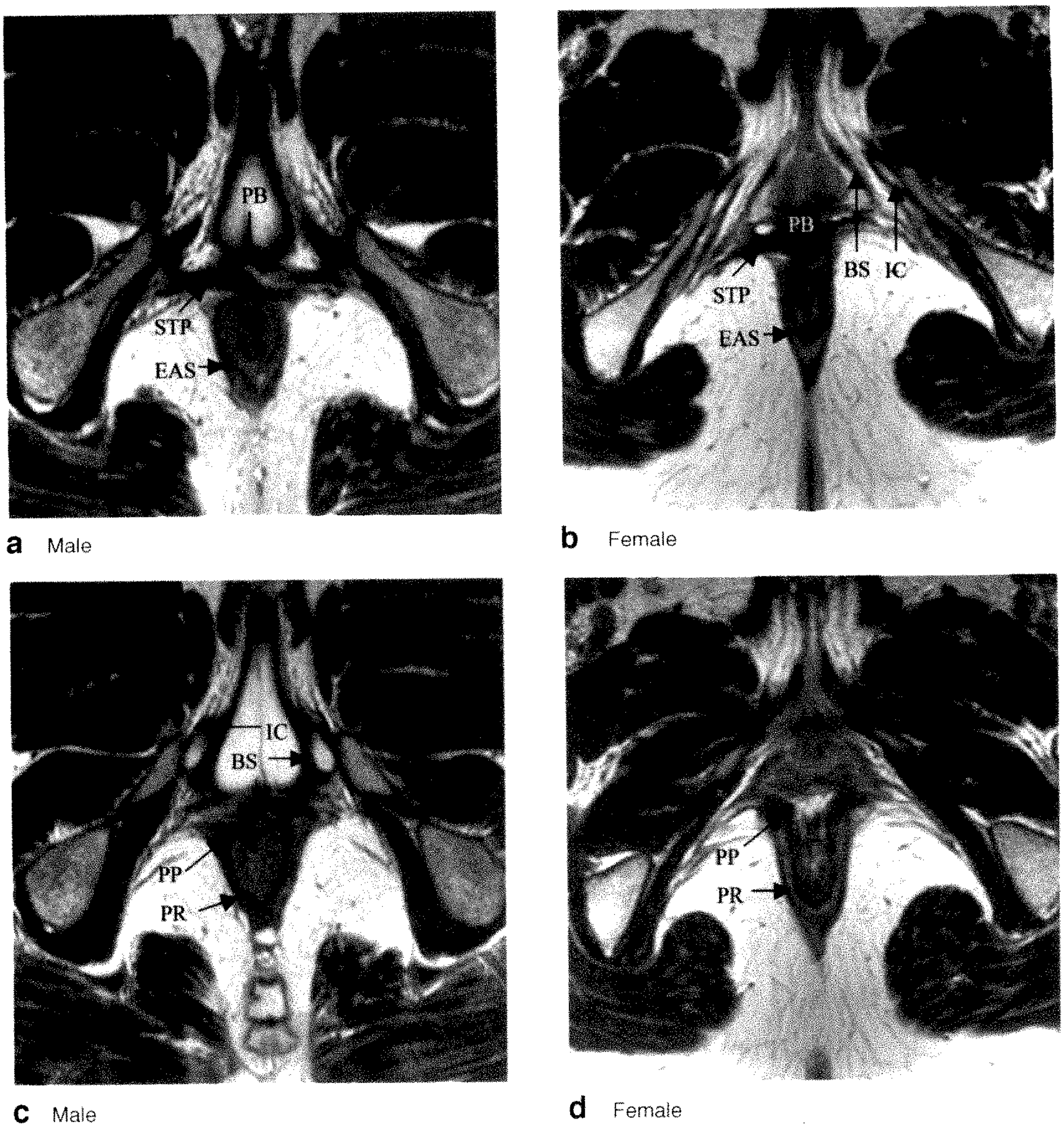
The anococcygeal body was defined in the sagittal plane by the pubococcygeal tendon cranially and the attachment of the posterior fibres of the EAS caudally. It was more or less elliptical (*Fig. 2a,b*).

Discussion

The changing configuration of the different parts of the anal canal and perianal structures requires multiple measurements at different levels and different dimensions for accurate description. Sex differences need to be taken into account and anatomical structures must be intact and undisturbed when studying normal anatomy. To the authors' knowledge, this is the first imaging study of the anal canal and perianal structures that meets all these requirements.

The anal canal was found to be asymmetrical in the sagittal plane. It had approximately the same length anteriorly and posteriorly, but was longer in the mid-coronal plane because of a longer EAS. Absolute measurements of anal canal length in the mid-coronal plane were similar to those in a previous report using the same technique[11] but smaller than those found when using MRI with an endocoil[6,8]. The endoanal coil possibly elongates the anal canal.

The lateral part of the female anal canal was longer than that of the male. Rociu *et al.*[8] did not find a difference in lateral anal canal length between the 50 men and 50 women



a Male

b Female

c Male

d Female

Fig. 3 Axial phased-array magnetic resonance images of the anal canal and perianal structures; **a** male and **b** female anatomy at the mid-anal level, **c** male and **d** female anatomy at the proximal anal level. BS, bulbospongiosus; EAS, external anal sphincter; IC, ischiocavernosus; PB, perineal body; PP, puboperinealis; PR, puborectalis; STP, superficial transverse perineal muscle

examined. The anterior EAS was significantly shorter in women than in men, confirming other reports[5,8]. The median length and thickness of the female anterior EAS were 11 and 3 mm respectively. The median sectional area of the anterior EAS is therefore only 33 mm^2. These small dimensions explain why a relatively small obstetrical tear may have a devastating effect on faecal continence and why it can be very difficult to identify the EAS while performing a primary or secondary sphincter repair after an obstetrical injury.

The anterior EAS occupied only 30 per cent of the female anal canal. Because the puborectalis sling is open anteriorly, the cranial 70 per cent of the anterior anal canal is not covered by striated muscle, forming an anatomical 'gap'. Differentiating this gap from a sphincter defect may be difficult during anal endosonography and may, in inexperienced hands, be a cause of false-positive reporting of anterior EAS defects. Laterally, the superficial EAS formed a double layer, reaching more caudally than its anterior or posterior parts.

Table 2 Sex differences in the dimensions of perianal structures

	Median (range) dimension (mm)			
	Women ($n = 19$)	Men ($n = 14$)	95 per cent c.i.	P*
Perineal body				
Length	12 (6–19)	9 (4–16)	0 to 6	0·03
Thickness	8 (4–12)	5 (2–6)	3 to 6	< 0·001
Width	13 (7–24)	9 (5–13)	2 to 8	0·02
STP muscle				
Length	25 (18–40)	18 (12–20)	6 to 13	< 0·001
Thickness	3 (2–6)	3 (2–6)	− 1 to 1	n.s.
Width	18 (10–26)	16 (10–24)	− 4 to 3	n.s.
Bulbospongiosus				
Thickness	2 (1–3)	3 (2–5)	− 2 to − 1	< 0·001
Ischiocavernosus				
Thickness	2 (1–4)	2 (2–4)	0	n.s.
Anococcygeal body				
Length	28 (14–39)	25 (18–32)	− 2 to 7	n.s.
Thickness	36 (23–51)	35 (22–40)	− 2 to 7	n.s.

c.i., confidence interval of median differences between sexes; STP, superficial transverse perineal muscle; n.s. not significant. *Mann–Whitney *U* test for comparisons between sexes

The EAS has previously been subdivided by anatomical dissection into three parts: subcutaneous, superficial and deep. Other investigators have distinguished only two parts, subcutaneous and deep[1]. MRI has not resolved this question as both trilaminar[13] and bilaminar[6,8] arrangements of the EAS have been described. In this study, the EAS could be subdivided into a deep and superficial part in most individuals, although a clear demarcation was often absent.

Williams *et al.*[5] described an overlap between the EAS and the puborectalis. In the present study such an overlap was recognized in only 30 per cent of individuals.

The term puboperinealis is not yet established in the surgical literature. It is the medial compartment of the puborectalis anterolateral to the anal canal. The puboperinealis has a rounded, triangular shape on both MRI and endoanal ultrasonography. It is closely related to the bladder base and membranous urethra. The left and right puboperinealis are sutured together when performing an 'anterior levatorplasty' procedure. It has been suggested that this procedure, in relation to radical prostatectomy, leads to a distortion of the puborectalis sling, thereby interfering directly with faecal continence[7].

In both men and women, the perineal body was closely related to the EAS and the different perineal muscles, often making the exact definition of this complex structure difficult. This may be the main reason for the wide range of normal values found. Nevertheless, the present findings correspond well with the anatomy of the perineal body as described by Oh and Kark[2] using anatomical dissection and histological sections. The perineal body was larger in women than in men and was located more anteriorly, closely related to the posterior and distal vaginal wall. It may serve as protection for the anterior EAS during childbirth. The role of obstetrical damage to the perineal body in the development of faecal incontinence has not been established and needs further study. Recently, the idea of specific repair of the perineal body after perineal injury has gained renewed attention[14].

Hussain *et al.*[6] described the female superficial transverse perineal muscle as a shield. The present authors have confirmed the presence of lateral and caudal extensions of the superficial transverse perineal muscle in both men and women. These extensions insert bilaterally into the ischiopubic bones and are centrally connected to the perineal body. They may serve as a bony anchor for all perineal structures. Their role in the pathogenesis of rectocele needs to be examined.

The anorectal junction (the caudal and dorsal bend in the anorectum) was formed by the puborectal muscle. It may therefore be appropriate to replace the term 'puborectalis' with 'puborectoanalis', as suggested by Wendell-Smith[15].

An important advantage of phased-array MRI over endoanal MRI and endoanal ultrasonography is its wider field of view. A single examination provides images of the entire lower pelvic region; not only the anal canal and surrounding structures are imaged, but also the bladder, urethra, prostate, uterus, vagina, cervix, rectum, levator ani, rectovesical septum, rectovaginal septum, retrorectal and supralevator space. This is important when examining patients with anorectal dysfunction because phased-array MRI has the potential to detect anal sphincter injury, rectocele, cystocele, enterocele and uterine prolapse. This aspect needs further study.

Acknowledgements

The authors thank Professor C. G. M. I. Baeten, who initiated the research, and E. Lemaire for invaluable help during the acquisition and preparation of the magnetic resonance images.

References

1 Oh C, Kark AE. Anatomy of the external anal sphincter. *Br J Surg* 1972; **59:** 717–23.

2 Oh C, Kark AE. Anatomy of the perineal body. *Dis Colon Rectum* 1973; **16:** 444–54.

3 Shafik A. A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation.

The external anal sphincter: a triple-loop system. *Invest Urol* 1975; **12:** 412–19.

4 Law PJ, Bartram CI. Anal endosonography: technique and normal anatomy. *Gastrointest Radiol* 1989; **14:** 349–53.

5 Williams AB, Cheetham MJ, Bartram CI, Halligan S, Kamm MA, Nicholls RJ *et al.* Gender differences in the longitudinal pressure profile of the anal canal related to anatomical structure as demonstrated on three-dimensional anal endosonography. *Br J Surg* 2000; **87:** 1674–9.

6 Hussain SM, Stoker J, Lameris JS. Anal sphincter complex: endoanal MR imaging of normal anatomy. *Radiology* 1995; **197:** 671–7.

7 Myers RP, Cahill DR, Devine RM, King BF. Anatomy of radical prostatectomy as defined by magnetic resonance imaging. *J Urol* 1998; **159:** 2148–58.

8 Rociu E, Stoker J, Eijkemans MJ, Lameris JS. Normal anal sphincter anatomy and age- and sex-related variations at high-spatial-resolution endoanal MR imaging. *Radiology* 2000; **217:** 395–401.

9 Tan IL, Stoker J, Zwamborn AW, Entius KA, Calame JJ, Lameris JS. Female pelvic floor: endovaginal MR imaging of normal anatomy. *Radiology* 1998; **206:** 777–83.

10 Beets-Tan RGH, Morren GL, Beets GL, Kessels AGH, el Naggar K, Lemaire E *et al.* Measurement of anal sphincter muscles: endoanal US, endoanal MR imaging, or phased-array MR imaging? A study with healthy volunteers. *Radiology* 2001; **220:** 81–9.

11 Beets-Tan RG, Beets GL, van der Hoop AG, Borstlap AC, van Boven H, Rongen MJ *et al.* High-resolution magnetic resonance imaging of the anorectal region without an endocoil. *Abdom Imaging* 1999; **24:** 576–81.

12 Federative Committee on Anatomical Terminology. *Terminologia Anatomica: International Anatomical Terminology.* Stuttgart: Federative Committee on Anatomical Terminology, 1998.

13 deSouza NM, Puni R, Zbar A, Gilderdale DJ, Coutts GA, Krausz T. MR imaging of the anal sphincter in multiparous women using an endoanal coil: correlation with *in vitro* anatomy and appearances in fecal incontinence. *AJR Am J Roentgenol* 1996; **167:** 1465–71.

14 Veronikis DK, Nichols DH, Spino C. The Noble–Mengert–Fish operation revisited: a composite approach for persistent rectovaginal fistulas and complex perineal defects. *Am J Obstet Gynecol* 1998; **179:** 1411–16.

15 Wendell-Smith CP. Anorectal nomenclature: fundamental terminology. *Dis Colon Rectum* 2000; **43:** 1349–58.

Original article

Estimating the benefits of adjuvant systemic therapy for women with early breast cancer

M. Grogan, L. Tabar*, B. Chua, H.-H. Chen† and J. Boyages

New South Wales Breast Cancer Institute, Westmead Hospital, University of Sydney, Westmead, New South Wales, Australia, *Department of Mammography, Central Hospital, Falun, Sweden and †Department of Epidemiology, College of Public Health, Taiwan University, Taipei, Taiwan
Correspondence to Professor J. Boyages, New South Wales Breast Cancer Institute, PO Box 143, Westmead, New South Wales 2145, Australia
(e-mail: johnb@bci.org.au)

Background: Prognostic factors are commonly used to help identify women with node-negative breast cancer at high risk of recurrence. Although many are available, knowing which risk factor or combination of factors to use to estimate prognosis for an individual woman is often difficult. This study documented the baseline prognoses for a group of women with node-negative breast cancers, and estimated the potential benefits of adjuvant systemic therapy.

Methods: Ten-year, actuarial, cause-specific survival based on tumour size and histological grade using data from the Swedish Two-County Trial of mammographic screening was calculated for 1200 women with node-negative cancers of less than 30 mm diameter. The benefits of adjuvant systemic therapy for these women were then estimated using the published odds reductions in death from adjuvant systemic therapy from the Early Breast Cancer Trialists' Collaborative Group overview.

Results: The absolute 10-year survival benefits for subgroups of women based on tumour size and histological grade were estimated for women aged under 50 years by the addition of chemotherapy, and over 50 years by the addition of tamoxifen and/or chemotherapy.

Conclusion: Decisions about adjuvant systemic therapy in women with node-negative breast cancer need to be individualized, taking into account treatment efficacy and toxicity. The quantitative methods presented in this paper facilitate such decisions.

Paper accepted 26 June 2001

British Journal of Surgery 2001, 88, 1513–1518

Introduction

A worldwide overview of all randomized clinical trials assessing the benefits of adjuvant systemic therapy has shown that adjuvant cytotoxic chemotherapy and/or hormonal therapy increased disease-free and overall survival for women with stage I or II breast cancer. Although the proportional reduction in the odds of recurrence or death from adjuvant systemic therapy was similar for women with node-positive or node-negative disease, the absolute improvement in disease-free and overall survival varied between subgroups of women and with the types of adjuvant systemic therapy[1,2].

Adjuvant systemic therapy for women with node-positive breast cancer is justified because of the high risk of subsequent metastatic disease and the absolute survival benefit of up to 10 per cent from treatment[3]. However, 70–95 per cent of women with node-negative disease remain disease free 10 years after local therapy. It is important to avoid the morbidity and cost of adjuvant systemic therapy for women at low risk of recurrence and to identify high-risk, node-negative women who may benefit from adjuvant systemic therapy.

Prognostic factors are used commonly to help identify women with node-negative breast cancer at high risk of recurrence. Although many potentially useful prognostic markers are available, knowing which ones to use or how to integrate them to estimate prognosis is often difficult. It is particularly difficult to estimate prognosis for a woman whose tumour contains both favourable and unfavourable prognostic features. In a multidisciplinary setting, it is possible that the information that women receive regarding prognosis and benefits of adjuvant systemic therapy may vary from one clinician to another, and be given with different emphasis.

Although there are limitations in using conventional prognostic factors such as tumour size, histological grade and oestrogen receptor (ER) status to estimate prognosis, the main advantages relate to their routine availability and low cost. A better understanding of prognosis using conventional pathological predictors of outcome, particularly for small, screen-detected cancers, and the development of tools to estimate outcomes (with or without systemic therapy) should help to make decisions about adjuvant therapy[3,4].

Patients and methods

The Swedish Two-County Trial of screening, published in 1985, reported breast cancer mortality rates for women aged 40–74 years who were invited to screening. A total of 2459 cancers was diagnosed, 1419 in the invited group and 1040 in the control group[5,6]. Tumour size was determined histologically and histological grade was scored by one pathologist in each county according to the Scarff–Bloom–Richardson grading system[7,8]. The causes of death were examined by a panel of investigating clinicians; causes other than breast cancer were treated as censored observations in the survival analysis.

The two-county study reported 10-year, actuarial, cause-specific survival rates for 1200 women with node-negative breast cancer less than 30 mm in diameter, who did not receive adjuvant systemic therapy, according to tumour size and histological grade[9]. These data were the basis of the model that was developed to assist in estimating the benefits of adjuvant systemic therapy. The cause-specific survival estimates were adjusted using the published odds reductions in death from adjuvant tamoxifen or chemotherapy from the Early Breast Cancer Trialists' Collaborative Group overview. Then, the absolute benefit of adjuvant systemic therapy in reducing breast cancer mortality rate[1,2] for women with breast cancer was estimated, using the proportional reduction in the odds of death at 10 years that adjuvant hormonal and cytotoxic chemotherapy provided. The upper limit of 30 mm tumour diameter was chosen because most centres would probably recommend systemic therapy for women with larger tumours, irrespective of histological grade. Moreover, these women with breast cancer were diagnosed and treated during a period when adjuvant chemotherapy was not given.

Follow-up data were updated to December 1998. The proportional reductions in the odds of death from hormonal and cytotoxic chemotherapy and associated confidence intervals were based on the 1995 Early Breast Cancer Trialists' meta-analysis of clinical trials (published in 1998)[1]. The Early Breast Cancer Trialists' Collaborative Group stated that 'the proportional risk reductions can be used to provide statistically stable estimates of 10-year absolute risk reductions'[10].

The absolute, cause-specific survival benefit from systemic therapy was calculated by subtracting the percentage 10-year survival from 100 per cent (and therefore determining the 10-year case fatality rate) and multiplying the difference by the proportional reduction in mortality (± its confidence interval) due to the adjuvant therapy. For instance, assuming that the cause-specific survival rate for a particular group of women was 80 per cent, the fatality rate was therefore 20 per cent and a 25 per cent (1/4) reduction in the odds of death equated with a 5 per cent absolute benefit (20 per cent × 1/4). Similar calculations were performed for the upper and lower confidence intervals. For the purpose of this study, an absolute cause-specific survival benefit of 3 per cent was used as an arbitrary threshold to identify subgroups of women who would benefit from adjuvant therapy.

Results

Table 1 documents the 10-year, actuarial, cause-specific survival based on tumour size and histological grade, using data collected for women with node-negative breast cancer in the Swedish Two-County Trial. The 10-year, cause-specific mortality rate increased with pathological tumour size. Within each size group, grade 3 tumours were associated with a higher mortality rate than grade 1 or 2 tumours.

Table 2 shows the estimated survival benefit of adjuvant chemotherapy for women with node-negative breast cancer aged under 50 years at diagnosis by ER status. The reduction in the odds of death for ER-positive women was 20 ± 10 per cent; for ER-negative women it was 35 ± 9 per cent[1]. The highest proportional reduction in the odds of death occurred for ER-negative women, consistent with

Table 1 Effects of pathological tumour size and grade on 10-year actuarial survival for women with node-negative breast cancer, aged 40–75 years, in the Swedish Two-County Trial

Tumour size (mm)	Histological grade	No. of patients	10-year cause-specific survival (%)
1–9	1	131	99·2
	2	115	97·2
	3	39	91·9
10–14	1	129	96·7
	2	149	95·1
	3	81	88·3
15–19	1	79	97·1
	2	103	91·8
	3	106	85·6
20–29	1	45	88·1
	2	101	79·2
	3	122	76·6

Table 2 Estimated survival benefit of chemotherapy for women aged less than 50 years with node-negative breast cancer of known oestrogen-receptor status

Tumour size (mm)	Tumour grade	10-year survival (%)	Absolute 10-year survival benefit (%)*	
			ER negative†	ER positive‡
1–9	1	99·2	0·3 (0·2–0·4)	0·2 (0·1–0·2)
	2	97·2	1·0 (0·7–1·2)	0·6 (0·3–0·8)
	3	91·9	2·8 (2·1–3·6)	1·6 (0·8–2·4)
10–14	1	96·7	1·2 (0·9–1·5)	0·7 (0·3–1·0)
	2	95·1	1·7 (1·3–2·2)	1·0 (0·5–1·5)
	3	88·3	4·1 (3·0–5·1)	2·3 (1·2–3·5)
15–19	1	97·1	1·0 (0·8–1·3)	0·6 (0·3–0·9)
	2	91·8	2·9 (2·1–3·6)	1·6 (0·8–2·5)
	3	85·6	5·0 (3·7–6·3)	2·9 (1·4–4·3)
20–29	1	88·1	4·2 (3·1–5·2)	2·4 (1·2–3·6)
	2	79·2	7·3 (5·4–9·2)	4·2 (2·1–6·2)
	3	76·6	7·1 (6·1–10·3)	4·7 (2·3–7·0)

*Values are median (range). †Odds reduction in mortality 35 ± 9 per cent; ‡odds reduction in mortality 20 ± 10 per cent. ER, oestrogen receptor

Table 3 Estimated survival benefit of chemotherapy for women aged 50 years or more with node-negative breast cancer, by age at diagnosis

Tumour size (mm)	Tumour grade	10-year survival (%)	Absolute 10-year survival benefit (%)*	
			Age 50–59 years†	Age 60–69 years‡
1–9	1	99·2	0·4 (0·1–0·1)	0·1 (0·0–0·1)
	2	97·2	0·4 (0·3–0·5)	0·2 (0·1–0·3)
	3	91·9	1·1 (0·8–1·5)	0·6 (0·3–1·0)
10–14	1	96·7	0·5 (0·3–0·6)	0·3 (0·0–0·4)
	2	95·1	0·7 (0·5–0·9)	0·4 (0·2–0·6)
	3	88·3	1·6 (1·2–2·1)	0·9 (0·5–1·4)
15–19	1	97·1	0·4 (0·5–2·5)	0·2 (0·1–0·3)
	2	91·8	1·1 (1·5–7·1)	0·7 (0·3–1·0)
	3	85·6	2·0 (2·6–12·4)	1·2 (0·6–1·7)
20–29	1	88·1	1·7 (2·1–10·2)	1·0 (0·5–1·4)
	2	79·2	2·9 (3·7–17·9)	1·7 (0·8–2·5)
	3	76·6	3·3 (4·2–20·1)	1·9 (0·9–2·8)

*Values are median (range). †Odds reduction in mortality 14 ± 4 per cent; ‡odds reduction in mortality 8 ± 4 per cent

previous reports that ER-negative tumours may be particularly sensitive to chemotherapy[11]. *Table 2* also shows that a median absolute cause-specific survival benefit of at least 3 per cent would apply for women with ER-negative tumours of 15 mm or more in diameter and histological grade 2 or 3.

Table 3 shows the estimated cause-specific survival benefit of adjuvant chemotherapy for women with node-negative breast cancer aged at least 50 years at diagnosis, by two age cohorts (50–59 and 60–69 years). The improvements in survival were greater for younger (aged 50–59 years) than older (60–69 years) postmenopausal women: 14 ± 4 *versus* 8 ± 4 per cent. These reductions in the odds of death were obtained from Figure 2 of the chemotherapy overview[1].

Table 4 shows the estimated benefit of adjuvant chemotherapy for women with node-negative breast cancer aged at least 50 years at diagnosis by ER status. Similar to women aged under 50 years, the mortality reduction was largest for women with ER-negative tumours. The reduction in the odds of death was 9 ± 5 per cent for ER-positive women and 17 ± 6 per cent for women with ER-negative tumours. These reductions in the odds of death were obtained from Figure 5 of the chemotherapy overview[1].

Table 5 shows the estimated benefit of adjuvant tamoxifen for women with node-negative breast cancer, aged 50 years or older, with known ER status. The reduction in the odds of death used was 25 ± 5 per cent for women with ER-positive tumours. These reductions were obtained from

Table 4 Estimated survival benefit of chemotherapy for women aged 50 years or more with node-negative breast cancer of known oestrogen-receptor status

Tumour size (mm)	Tumour grade	10-year survival (%)	Absolute 10-year survival benefit (%)*	
			ER negative†	ER positive‡
1–9	1	99·2	0·1 (0·1–0·2)	0·1 (0·0–0·1)
	2	97·2	0·5 (0·3–0·6)	0·3 (0·1–0·4)
	3	91·9	1·4 (0·9–1·9)	0·7 (0·3–1·1)
10–14	1	96·7	0·6 (0·4–0·8)	0·3 (0·1–0·5)
	2	95·1	0·8 (0·5–1·1)	0·4 (0·2–0·7)
	3	88·3	2·0 (1·3–2·7)	1·1 (0·5–1·6)
15–19	1	97·1	0·5 (0·3–0·7)	0·3 (0·1–0·4)
	2	91·8	1·4 (0·9–1·9)	0·7 (0·3–1·1)
	3	85·6	2·4 (1·6–3·3)	1·3 (0·6–2·0)
20–29	1	88·1	2·0 (1·3–2·7)	1·1 (0·5–1·7)
	2	79·2	3·5 (2·3–4·8)	1·9 (0·8–2·9)
	3	76·6	4·0 (2·6–5·4)	2·1 (0·9–3·3)

*Values are median (range). †Odds reduction in mortality 17 ± 6 per cent; ‡odds reduction in mortality 9 ± 5 per cent. ER, oestrogen receptor

Table 5 Estimated survival benefit of tamoxifen for women aged 50 years or more with node-negative breast cancer of known oestrogen-receptor status

Tumour size (mm)	Tumour grade	10-year survival (%)	Absolute 10-year survival benefit (%)*	
			ER negative†	ER positive‡
1–9	1	99·2	0·0 (0·0–0·1)	0·2 (0·2–0·2)
	2	97·2	0·2 (0·1–0·3)	0·7 (0·6–0·8)
	3	91·9	0·5 (0·2–0·8)	2·0 (1·6–2·4)
10–14	1	96·7	0·2 (0·1–0·3)	0·8 (0·7–1·0)
	2	95·1	0·3 (0·1–0·5)	1·2 (1·0–1·5)
	3	88·3	0·7 (0·2–1·2)	2·9 (2·3–3·5)
15–19	1	97·1	0·2 (0·1–0·3)	0·7 (0·6–0·9)
	2	91·8	0·5 (0·2–0·8)	2·1 (1·6–2·5)
	3	85·6	0·9 (0·3–1·4)	3·6 (2·9–4·3)
20–29	1	88·1	0·7 (0·2–1·2)	3·0 (2·4–3·6)
	2	79·2	1·2 (0·4–2·1)	5·2 (4·2–6·2)
	3	76·6	1·4 (0·5–2·3)	5·9 (4·7–7·0)

*Values are median (range). †Odds reduction in mortality 6 ± 4 per cent; ‡odds reduction in mortality 25 ± 5 per cent. ER, oestrogen receptor

Figure 3 of the tamoxifen overview in which it was estimated that 96 per cent of women had an ER-positive tumour and 82 per cent were 50 years of age or older, at diagnosis[2]. For the present analysis, the overall fatality reduction of 6 ± 4 per cent among the 8000 women with ER-negative tumours was used, irrespective of tamoxifen duration. *Table 5* shows that, for women aged at least 50 years with ER-positive tumours, a median absolute cause-specific survival benefit of over 3 per cent was estimated for tumours of 10–19 mm and grade 3, or 20 mm or larger and any grade. However, given tamoxifen's association with few side-effects compared with adjuvant chemotherapy, and its impact in reducing contralateral breast cancer, the median threshold could be lowered in this setting and treatment could be omitted only for women with small grade 1 tumours. For women with ER-negative tumours, no subgroup reached the median threshold of 3 per cent.

The overview also presented fatality data for the use of chemotherapy in addition to tamoxifen. For women aged 50–69 years, the odds reduction in death from chemotherapy and tamoxifen compared with chemotherapy alone was 11 ± 4 per cent. Using the data in *Table 5*, the additional benefit of chemotherapy for women with ER-positive tumours was up to 0·9 per cent for tumours of diameter 20–29 mm.

Discussion

Predicting the clinical course of women with node-negative breast cancer is difficult. Some women will remain disease free after local therapy, whereas others will die from recurrent disease. Women at low risk of recurrence may, after a full discussion, choose to avoid the toxicities of adjuvant systemic therapy, while those at high risk of recurrence may choose to accept them because of a greater benefit. The desire to individualize the treatment of women with node-negative breast cancer has led to the use of prognostic factors to separate women into groups with different risks of recurrence. Although prognostic factors are useful in predicting short-term survival, they are of limited use in predicting long-term outcome. Many long-term survivors from breast cancer had 'favourable histology' but also had unfavourable prognostic characteristics, such as large tumour size and/or nodal involvement[12].

In the present study, the cause-specific survival data from the Swedish two-county mammographic screening study were used to estimate the benefits of adjuvant systemic therapy. The 10-year cause-specific survival of women who had mammographically or clinically detected breast carcinomas, and who were treated by local therapy alone, was based on pathological tumour size and grade[13]. The importance of size as a prognostic factor is underscored by the finding that pathological grade deteriorated with increasing tumour size. Although there were discordances between the two counties in the proportions of grades 1, 2 and 3 tumours, the relationship of grade with size and nodal status with survival was almost identical[14].

The Swedish data were used because of their long-term follow-up, integrated nodal status and grade; these data were based on a population that had predominantly node-negative tumours of less than 30 mm diameter. Furthermore, the use of 10-year, cause-specific survival data as the basis of the model enabled the estimation of the impact of adjuvant therapy on breast cancer mortality alone, and avoided the confounding effects of natural deaths.

Several steps are necessary when making a decision about treatment. Initially, the clinician must estimate an individual patient's prognosis based on all available information. If the pathological tumour size and grade are known, then the 10-year cause-specific survival can be estimated from *Table 1*.

After cause-specific survival has been estimated, all potential treatment options need to be considered. The type of adjuvant therapy to be considered is influenced by the woman's age, menopausal status and hormone receptor status. The efficacy of different adjuvant therapies needs to be determined. The reduction in the odds of death and subsequent absolute increase in 10-year cause-specific survival attributable to different therapies can be estimated from *Tables 2–5*.

Lastly, the benefits of treatment must be weighed against the cost and toxicity of therapy. The known potential toxicities of cytotoxic chemotherapy and tamoxifen have been well described. The short-term toxic effects of chemotherapy include nausea, vomiting, alopecia, mucositis and neutropenia. These are generally well tolerated and are reversible. However, the long-term complications are potentially more serious and include the possibility of premature ovarian failure and the induction of early menopause. If an anthracycline is used, there remains the possibility of cardiomyopathy. Tamoxifen may induce hot flushes and other menopausal symptoms, and is also associated with a small risk of thromboembolism and endometrial cancer.

For some women, specific types of therapy-induced toxicity may be sufficient reason to reject adjuvant therapy, whereas others may feel that the toxicity of therapy is acceptable in return for the possibility of living longer. Similarly, the threshold of risk for relapse and death for which a therapy becomes worthwhile will vary from patient to patient depending on the levels of risk and benefit that a woman is willing to accept.

While it is possible to recommend specific thresholds of risk above which adjuvant therapy should be recommended, women should be involved in making decisions when the benefits are communicated in ways that are easy to comprehend and not misleading.

Acknowledgements

The New South Wales Breast Cancer Institute receives financial support from the New South Wales Health Department. The authors thank Ms Josette Banks, Mrs Dorothy Smith and Ms Cathie Lyons for their assistance in preparation of the manuscript, and Dr Greg Heard for editorial comments. Dr David Roder, Professor Allan Langlands, Professor Lars Rutqvist and Ms Elaine Beller are also thanked for critical review of earlier drafts of this document.

References

1 Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 352: 930–42.

2 Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451–67.

3 Siminoff LA, Ravdin PM, Gerson N, Davis G, Mercer MB, Parker H *et al.* Impact of a personal computer based tool for providing individualized estimates of outcomes for patients with early breast cancer. *Proceedings of the American Society of Clinical Oncology* 1998; **17:** 105a.

4 Ravdin PM. A practical view of prognostic factors for staging, adjuvant treatment planning, and as baseline studies for possible future therapy. *Hematol Oncol Clin North Am* 1994; **8:** 197–211.

5 Tabar L, Duffy SW, Burhenne LW. New Swedish breast cancer detection results for women aged 40–49. *Cancer* 1993; **72**(Suppl 4)**:** 1437–48.

6 Tabar L, Dean PB, Kaufman CS, Duffy SW, Chen H-H. A new era in the diagnosis of breast cancer. *Surg Oncol Clin N Am* 2000; **9:** 233–77.

7 Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. A study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957; **11:** 359–77.

8 Scarff RW, Torloni H. *Histological Typing of Breast Tumours. International Histological Classification of Tumours No. 2.* Geneva: World Health Organisation, 1968.

9 Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM. Breast cancer treatment and natural history: new insights from results of screening. *Lancet* 1992; **339:** 412–14.

10 Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992; **339:** 71–85.

11 Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London. Adjuvant ovarian ablation *versus* CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. *Lancet* 1993; **341:** 1293–8.

12 Langlands AO. Prognostic factors and the curability of breast cancer. *Aust N Z J Surg* 1995; **65:** 630–3.

13 Rubin E, Mazur MT, Urist MM, Maddox WA. Clinical, radiographic, and pathologic correlation of atypical hyperplasia, ductal carcinoma *in situ*, and ductal carcinoma *in situ* with micro-invasion. *Breast* 1993; **2:** 21–6.

14 Duffy SW, Tabar L, Fagerberg G, Gad A, Grontoft O, South MC *et al.* Breast screening, prognostic factors and survival: results from the Swedish two-county study. *Br J Cancer* 1991; **64:** 1133–8.

Original article

Prospective study of the effect of laparoscopic Nissen fundoplication on reflux mechanisms

J. W. A. Straathof, J. Ringers* and A. A. M. Masclee

Departments of Gastroenterology–Hepatology and *Surgery, Leiden University Medical Center, Leiden, The Netherlands
Correspondence to: Dr A. A. M. Masclee, Department of Gastroenterology–Hepatology, C4-P, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands (e-mail: A.A.M.Masclee@lumc.nl)

Background: Laparoscopic Nissen fundoplication effectively reduces acid reflux and reflux symptoms. Little is known about the effect on reflux mechanisms, especially on transient lower oesophageal sphincter relaxations (TLOSRs).

Methods: Twenty-seven patients were studied prospectively before and after laparoscopic Nissen fundoplication, by simultaneous recording of pH and lower oesophageal sphincter (LOS) characteristics using sleeve manometry. In all of the 27 patients the operation was judged successful, based on major improvement or resolution of reflux symptoms and acid reflux. Vagus nerve integrity was studied indirectly by the secretion of pancreatic polypeptide (PP) in response to insulin-induced hypoglycaemia.

Results: After fundoplication basal LOS pressure increased significantly from mean(s.e.m.) 13(1) to 22(1) mmHg ($P < 0{\cdot}001$). Laparoscopic Nissen fundoplication significantly decreased the frequency of TLOSR in the fasting period from mean(s.e.m.) 2·5(0·5) to 0·6(0·2) per h, and in the postprandial period from 4·0(0·4) to 1·3(0·3) per h ($P < 0{\cdot}01$). The percentage of TLOSRs associated with reflux also decreased significantly from 24(10) to 0(0) per cent in the fasting period and from 42(6) to 12(6) per cent in the postprandial period, before and after fundoplication respectively ($P < 0{\cdot}01$). After operation the PP response was abnormal in three patients, pointing to vagus nerve dysfunction. Postoperative TLOSR frequency and LOS pressure were no different between patients with and without vagus nerve dysfunction.

Conclusion: Laparoscopic Nissen fundoplication significantly increased fasting and postprandial LOS pressure and significantly decreased the rate of TLOSR. This resulted in a significant reduction in oesophageal acid exposure but postprandial LOS characteristics were preserved.

Paper accepted 20 June 2001

British Journal of Surgery 2001, **88**, 1519–1524

Introduction

Antireflux surgery is considered when patients with proven gastro-oesophageal reflux disease (GORD) are refractory to medical therapy[1]. The Nissen fundoplication is the most commonly applied antireflux procedure. Since the introduction of laparoscopic techniques, antireflux surgery has received renewed attention. Minimally invasive antireflux procedures provide excellent symptom relief with rapid recovery and low postoperative morbidity, assuming sufficient surgical expertise[2].

Several studies have shown that the most prevalent mechanism of reflux in patients with GORD and in healthy subjects is the transient lower oesophageal sphincter relaxation (TLOSR)[3–5]. Although antireflux procedures are frequently performed, the mechanism of action of antireflux surgery is poorly understood. Previous studies of open procedures have shown that Nissen fundoplication and partial (Belsey Mark IV) fundoplication reduce the frequency of TLOSR[6,7]. Although much has been published about the outcome after laparoscopic Nissen fundoplication in terms of symptom relief[8] and reflux control[9], the effect of laparoscopic Nissen fundoplication on TLOSR has not been studied.

In the present study, patients with GORD were investigated prospectively before and 6 months after laparoscopic Nissen fundoplication with emphasis on TLOSR as the major mechanism of reflux. Oesophageal pH and sleeve manometry were performed under fasting conditions and in response to a meal.

Patients and methods

Patients

Between January 1993 and December 1997, 75 patients underwent laparoscopic Nissen fundoplication as the primary antireflux procedure for GORD that was resistant to medical therapy. Twenty-seven of these patients agreed to participate in a prospective study evaluating the effect of the laparoscopic Nissen procedure on mechanisms of gastro-oesophageal reflux. All patients (11 men and 16 women; mean age 45 (range 21–72) years) had symptoms of gastro-oesophageal reflux such as heartburn, regurgitation, retrosternal pain or dysphagia. GORD was documented in all patients by endoscopy and/or by ambulatory 24-h pH monitoring. At this institution preoperative evaluation includes upper gastrointestinal endoscopy, oesophageal manometry, 24-h ambulatory pH monitoring and vagus nerve function test. Postoperative evaluation, including oesophageal manometry, 24-h ambulatory pH monitoring and vagus nerve function test, was performed 6 months after the operation.

Indications for antireflux surgery were the presence of reflux symptoms not responding sufficiently to prolonged medical treatment (more than 6 months) including proton pump inhibitors. Objective signs of reflux disease had to be present (endoscopic oesophagitis and/or abnormal 24-h oesophageal pH measurements).

The surgical procedure, laparoscopic Nissen fundoplication, was performed by one surgeon (J.R.). The operative technique entailed initial mobilization of the oesophagus and posterior hiatal repair. The gastric fundus was not routinely mobilized. The fundus was wrapped around the oesophagus, which was calibrated with a 42-Fr bougie within the oesophageal lumen, to enable construction of a floppy 360° fundoplication.

Mechanisms of gastro-oesophageal reflux were investigated in 27 patients before and 6–12 months after the operation. All patients were studied after an overnight fast. Medication was stopped at least 72 h before the study. Informed consent was obtained from each individual and the protocol was approved by the local research ethics committee.

Endoscopy

The severity of oesophagitis was graded endoscopically according to the criteria of Savary and Miller. Preoperative endoscopy showed oesophagitis grade 0 in six patients, grade I in eight patients, grade II in ten patients and grade III in three patients.

Twenty-four-hour pH monitoring

Twenty-four-hour ambulatory intraoesophageal pH monitoring was performed as described previously[10]. Gastro-oesophageal reflux was considered pathological when the oesophageal pH fell below 4 for 4·0 per cent or more of the total recording time[10]. Preoperative evaluation revealed abnormal 24-h pH measurements in 24 patients; in three patients reflux time was in the normal range but the patients had endoscopic signs of reflux disease (oesophageal pH below 4 for 0–4 per cent of the monitoring time).

Vagus nerve integrity

Vagus nerve integrity was measured indirectly by the secretion of plasma pancreatic polypeptide (PP) in response to insulin-induced hypoglycaemia[11,12]. PP was measured by a sensitive and specific radioimmunoassay[13]. A peak increment in plasma PP below 47 pmol/l is considered to be compatible with vagus nerve dysfunction[11].

Manometric and pH technique

The manometry catheter consisted of a multilumen silicon tube (outer diameter 5·0 mm) incorporating a 6-cm long sleeve sensor (Dentsleeve Property, Belair, South Australia, Australia). The manometry catheter was introduced through the nose into the oesophagus and positioned so that the sleeve sensor straddled the lower oesophageal sphincter (LOS). A glass pH electrode (Ingold, Urdorf, Germany) was positioned 5 cm above the upper margin of the LOS.

Study protocol

Experiments were started at 09.00 hours after an overnight fast. The subjects were studied in the upright position, sitting in a comfortable chair. They were not allowed to doze because of the effect of sleep on TLOSR. Oesophageal manometry and pH were recorded simultaneously during a 30-min fasting period and for 180 min after a standard breakfast consisting of 400 ml Nutridrink® (Nutricia, Zoetermeer, The Netherlands) containing 20 g protein, 26 g fat and 72 g carbohydrates (2520 kJ).

Lower oesophageal sphincter data and pH analysis

LOS tracings were analysed for LOS resting pressure and LOS relaxations including TLOSR. TLOSRs were defined according to Mittal *et al.*[14]. Gastro-oesophageal reflux episodes and the mechanisms of each reflux episode were scored using criteria described previously[7].

Statistical analysis

Data are expressed as mean(s.e.m.). Statistical analyses of TLOSR and reflux were performed using Wilcoxon's signed rank test and the Mann–Whitney *U* test. Differences in LOS pressure before and after operation and in response to meal ingestion were analysed using multiple analysis of variance. $P < 0.05$ was considered significant for all analyses.

Results

In all 27 patients the operation was judged successful, based on major improvement or absence of reflux symptoms and gastro-oesophageal acid reflux. One patient had severe dysphagia after operation. This patient is included in the data analysis. After the postoperative studies she underwent reoperation during which the wrap was dismantled.

Vagus nerve integrity

All patients had plasma PP peak increments in the normal range (above 47 pmol/l) before operation, with a mean value of 146(11) pmol/l. After fundoplication the PP response was normal in all but three patients who had PP peak values indicative of vagus nerve dysfunction (47 pmol/l or less). None the less, the LOS pressure and TLOSR frequency in these three patients were no different from those of the other patients, who had no signs of vagus nerve dysfunction. The mean postoperative plasma PP peak increment in patients with responses in the normal range was 121(10) pmol/l.

Twenty-four-hour oesophageal pH monitoring

Compared with preoperative values total reflux time during 24-h oesophageal pH measurement decreased significantly from 11·7(2·3) (range 2·1–49·2) to 0·8(0·3) (range 0–6·0) per cent ($P < 0.01$).

Lower oesophageal sphincter pressure

After fundoplication basal LOS pressure before a test meal increased significantly from 13(1) to 22(1) mmHg ($P < 0.001$) (*Fig. 1*). Before operation, LOS pressure was significantly decreased ($P < 0.05$) between 15 and 150 min after the start of the meal, reaching a minimum of 7(1) mmHg 30 min postprandially. After operation, meal ingestion reduced LOS pressure between 15 and 45 min postprandially, reaching a minimum of 17(2) mmHg at 30 min. Postprandial LOS pressures after operation were significantly higher than preoperative values ($P < 0.001$).

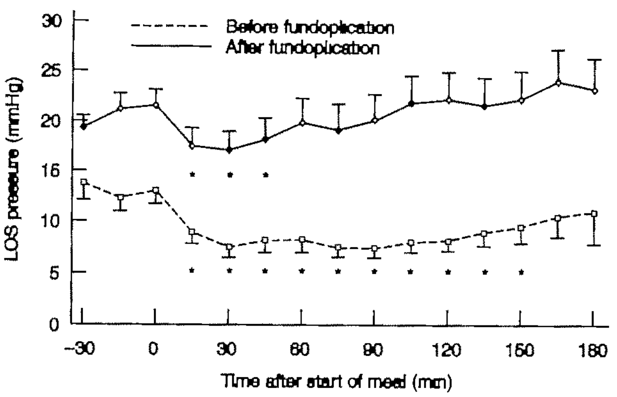


Fig. 1 Mean(s.e.m.) basal and postprandial lower oesophageal sphincter (LOS) pressure at the gastro-oesophageal junction before and after laparoscopic Nissen fundoplication in 27 patients with gastro-oesophageal reflux disease. $^*P < 0.05$ *versus* basal value (before meal) (Manova test)

Transient lower oesophageal sphincter relaxations

TLOSRs were identified in all patients before operation. However, after laparoscopic Nissen fundoplication, TLOSRs were registered in only 21 of the 27 patients. In six subjects only spontaneous LOS relaxations with incomplete LOS relaxation were identified (*Fig. 2*). All the postoperative TLOSRs had a residual LOS pressure of 2 mmHg or less, according to the definition of TLOSR. A total of 76 spontaneous LOS relaxations, which met all criteria for a TLOSR apart from reaching the intragastric nadir pressure, were observed after laparoscopic Nissen fundoplication. Residual pressures during these relaxations varied from 3 to 28 mmHg. According to the definition, these relaxations were not scored as TLOSRs.

The total number of TLOSRs recorded in all subjects decreased after operation from 47 to 11 in the fasting period and from 274 to 98 in the postprandial period. The frequency of TLOSRs in the fasting period and after the meal decreased significantly after operation ($P < 0.01$) (*Table 1*). Fundoplication not only reduced the number of TLOSRs but also significantly decreased the percentage of TLOSRs associated with gastro-oesophageal acid reflux in the fasting and postprandial period from 24(10) and 42(6) per cent respectively before operation, to 0(0) and 12(6) per cent respectively after operation ($P < 0.01$).

The mean duration of TLOSR was 18·4(0·5) s before fundoplication and decreased significantly to 16·0(1·1) s after fundoplication ($P < 0.05$). The preoperative and postoperative duration of TLOSRs accompanied by acid reflux (20·4(1·0) s) was significantly longer ($P < 0.001$) than that of TLOSRs without gastro-oesophageal acid reflux (16·6(0·5) s).

Mechanism of reflux

The total number of gastro-oesophageal reflux episodes was 284 before operation and 15 after operation (*Table 2*). The predominant mechanism of reflux was TLOSR: 43 per cent before and 60 per cent (nine of 15) after fundoplication.

Gastro-oesophageal reflux

Fundoplication significantly reduced the oesophageal acid exposure time in the basal period from 1·7(0·8) to 0(0) per

Table 1 Frequency of transient lower oesophageal sphincter relaxations in the fasting and postprandial period before and after laparoscopic Nissen fundoplication in 27 patients with gastro-oesophageal reflux disease

	Before operation	After operation
TLOSRs (no. per h)		
Basal	2·5(0·5)	0·6(0·2)*
Postprandial	4·0(0·4)	1·3(0·3)*
TLOSRs associated with reflux (%)		
Basal	24(10)	0(0)*
Postprandial	42(6)	12(6)*

Values are mean(s.e.m.). TLOSR, transient lower oesophageal sphincter relaxation. *$P < 0·01$ *versus* before operation (Mann–Whitney *U* test)

Table 2 Mechanism of gastro-oesophageal acid reflux for all reflux episodes observed during a total recording time of 85 h in 27 patients with gastro-oesophageal reflux disease before and after laparoscopic Nissen fundoplication

Mechanism of reflux	Before operation	After operation
TLOSR	123	9
Swallow-induced LOS relaxation	30	0
LOS pressure drift	17	1
Absent LOS pressure	49	0
Abdominal strain	53	0
Other (unexplained)	12	5
Total reflux episodes	284	15

Recording was for 190 min per patient, 30 min fasting and 160 min postprandial. LOS, lower oesophageal sphincter; TLOSR, transient lower oesophageal sphincter relaxation

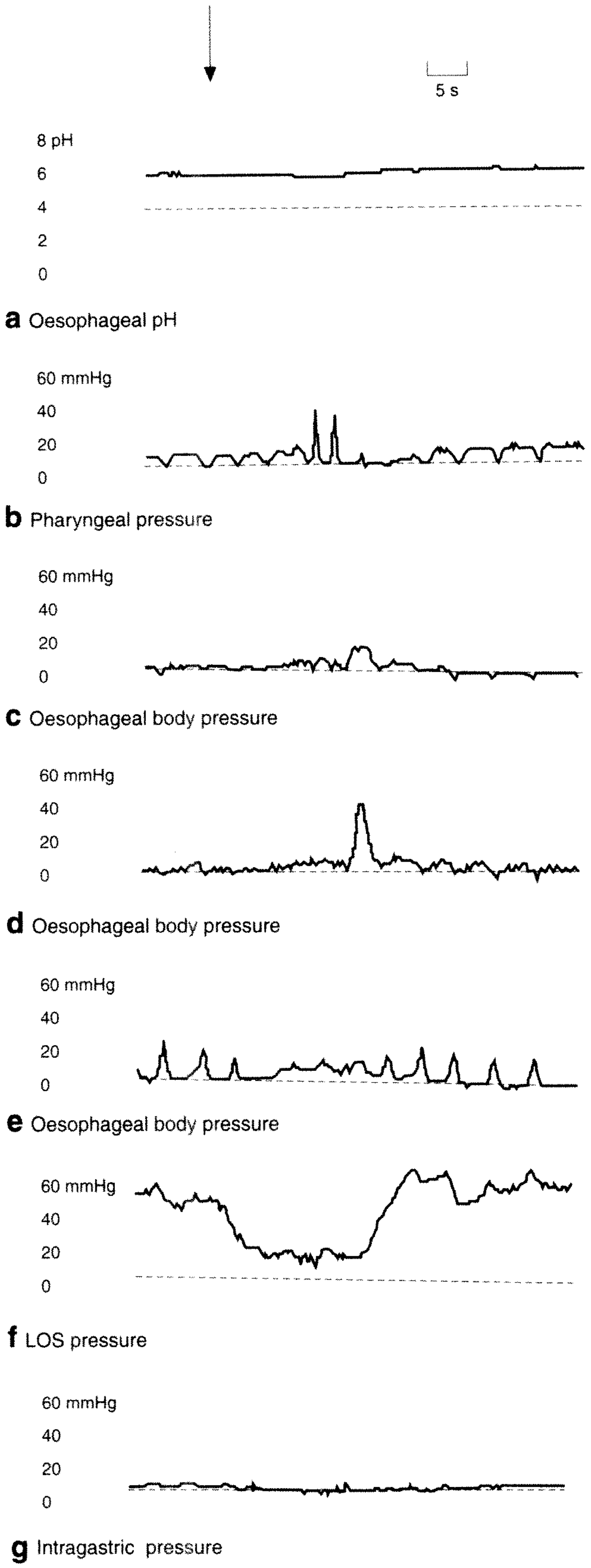


Fig. 2 Tracing of an 'incomplete' transient lower oesophageal sphincter relaxation (arrow) in a patient after laparoscopic Nissen fundoplication. The tracings show oesophageal pH (**a**), pharyngeal pressure (**b**), oesophageal body pressure (**c**–**e**), lower oesophageal sphincter (LOS) pressure (**f**) and intragastric pressure (**g**). The dotted line denotes intragastric pressure (parts **b**–**g**) or pH 4 (**a**). The LOS pressure does not decrease to intragastric pressure during a spontaneous LOS relaxation

cent ($P < 0{\cdot}01$) and in the postprandial period from 11·7(3·7) to 0(0) per cent ($P < 0{\cdot}01$). In addition, fundoplication significantly decreased the frequency of reflux episodes during fasting (1·3(0·6) per h before fundoplication *versus* 0·1(0·1) per h after operation) and in the postprandial period (9·1(1·7) *versus* 0·5(0·2) per h) ($P < 0{\cdot}01$).

Discussion

Laparoscopic Nissen fundoplication effectively reduces gastro-oesophageal reflux[15,16]. However, the effect of laparoscopic surgery on reflux mechanisms had not been studied previously. This study has shown that the number of TLOSRs is decreased both in the fasting and the postprandial state after laparoscopic Nissen fundoplication. These results are consistent with findings in a previous study of the effect of open Nissen fundoplication on the rate of TLOSR[6]. A study on the effect of partial fundoplication (Belsey Mark IV) on TLOSR also showed a postoperative reduction in the rate of TLOSR and a decrease in the percentage of TLOSRs associated with gastro-oesophageal acid reflux[7].

The mechanism by which laparoscopic Nissen fundoplication decreases the number of TLOSRs is not understood. Several factors may be involved. Distension of the proximal stomach, either by air insufflation, insufflation of a barostat bag or by meal ingestion, is a potent trigger for TLOSR. The frequency of TLOSR is related to the volume of the proximal stomach and the degree of fundic distension[17]. After Nissen fundoplication postprandial relaxation of the proximal stomach is impaired, i.e. after meal ingestion the maximum volume of the proximal stomach is significantly smaller in patients with Nissen fundoplication than in non-operated patients with GORD or healthy controls[18,19]. Therefore the decreased frequency of TLOSR after fundoplication may be related to impaired postprandial relaxation of the proximal stomach.

The vagus nerve is involved in the pathway through which TLOSRs are triggered. Vagotomy and atropine decrease the frequency of TLOSR[20,21]. After Nissen fundoplication vagus nerve dysfunction may occur in up to 30 per cent and lead to symptoms such as nausea, bloating or diarrhoea. Such symptoms were observed in patients who participated in this study. There was evidence of postoperative vagus nerve dysfunction in only three of the 27 subjects. The reduction in frequency of TLOSR after fundoplication does not therefore appear to result from vagus nerve dysfunction.

After fundoplication TLOSR with complete LOS relaxation reaching intragastric pressure occurred in 21 patients. However, in six subjects only incomplete spontaneous LOS relaxations occurred. The incomplete TLOSRs have all the characteristics required for a TLOSR apart from residual LOS pressure. Fundoplication not only influences the frequency of TLOSR but may also prohibit complete relaxation of the LOS during TLOSR or during swallowing.

Dysphagia is common in the early postoperative period and may be related to LOS dysfunction, especially incomplete LOS relaxation. In a recently published randomized clinical trial of open *versus* laparoscopic Nissen fundoplication the relative risk of postoperative dysphagia was in favour of open surgery[22], but LOS relaxation was not evaluated. Apart from acid reflux TLOSR also provides a mechanism for venting gas from the stomach, i.e. belching[23]. An impaired ability to belch is common after antireflux surgery. Johnsson *et al.*[24] noted that patients after 360° fundoplication with concomitant highly selective vagotomy did not exhibit TLOSR or common cavities in response to gastric distension. An absence of TLOSR may therefore be related to an inability to belch and may lead to gas bloat syndrome. The frequency of TLOSR decreased after laparoscopic Nissen fundoplication in all of the present patients but TLOSRs, both complete and incomplete, still occurred; this may be relevant for the physiological venting of air from the stomach.

In conclusion, laparoscopic Nissen fundoplication significantly increased fasting and postprandial LOS pressure and significantly decreased the rate of TLOSR. It significantly decreased oesophageal acid exposure and reduced mechanisms of reflux, but with preservation of postprandial LOS characteristics.

References

1 Anvari M, Allen C, Borm A. Laparoscopic Nissen fundoplication is a satisfactory alternative to long-term omeprazole therapy. *Br J Surg* 1995; **82:** 938–42.

2 McKernan JB, Champion JK. Minimally invasive antireflux surgery. *Am J Surg* 1998; **175:** 271–6.

3 Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. *Gut* 1988; **29:** 1020–8.

4 Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK *et al.* Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982; **307:** 1547–52.

5 Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC *et al.* Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980; **65:** 256–67.

6 Ireland AC, Holloway RH, Toouli J, Dent J. Mechanisms underlying the antireflux action of fundoplication. *Gut* 1993; **34:** 303–8.

7 Masclee AAM, Horbach JM, Ledeboer M, Lamers CBHW, Gooszen HG. Prospective study of the effect of the Belsey Mark-IV fundoplication on reflux mechanisms. *Scand J Gastroenterol* 1998; **33:** 905–10.

8 Bittner HB, Meyers WC, Brazer SR, Pappas TN. Laparoscopic Nissen fundoplication: operative results and short-term follow-up. *Am J Surg* 1994; **167:** 193–8.

9 Mathew G, Watson DI, Myers JC, Holloway RH, Jamieson GG. Oesophageal motility before and after laparoscopic Nissen fundoplication. *Br J Surg* 1997; **84:** 1465–9.

10 Masclee AAM, de Best ACAM, de Graaf R, Cluysenaer OJ, Jansen JBMJ. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to endoscopy. *Scand J Gastroenterol* 1990; **25:** 225–30.

11 Jansen EH, Horbach JMLM, Klamer M, Jansen JBMJ, Hopman WPM, Gooszen HG *et al.* Plasma pancreatic polypeptide response to insulin hypoglycaemia after Nissen fundoplication. *Scand J Gastroenterol* 1989; **24**(Suppl 171): 9–12.

12 Masclee AAM, Lamers CBHW. Effect of endoscopic sclerotherapy of esophageal varices on vagus nerve integrity. *J Hepatol* 1994; **21:** 724–9.

13 Lamers CBHW, Diemel CM, van Leer E, van Leusen R, Peetoom JJ. Mechanism of elevated serum pancreatic polypeptide concentrations in chronic renal failure. *J Clin Endocrinol Metab* 1982; **55:** 922–6.

14 Mittal RK, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995; **109:** 601–10.

15 Gotley DC, Smithers BM, Rhodes M, Menzies B, Branicki FJ, Nathanson L. Laparoscopic Nissen fundoplication: 200 consecutive cases. *Gut* 1996; **38:** 487–91.

16 Pursani KG, Sataloff DM, Zayas F, Castell DO. Evaluation of the antireflux mechanism following laparoscopic fundoplication. *Br J Surg* 1997; **84:** 1157–61.

17 Boulant J, Mathieu S, D'Amato M, Abergel A, Dapoigny M, Bommelaer G. Cholecystokinin in transient lower oesophageal sphincter relaxation due to gastric distension in humans. *Gut* 1997; **40:** 575–81.

18 Vu MK, Straathof JWA, van der Schaar PJ, Arndt JW, Ringers J, Lamers CBHW *et al.* Motor and sensory function of the proximal stomach in reflux disease and after laparoscopic Nissen fundoplication. *Am J Gastroenterol* 1999; **94:** 1481–9.

19 Wijnhoven BPL, Salet GAM, Roelofs JMM, Smout AJPM, Akkermans LMA, Gooszen HG. Function of the proximal stomach after Nissen fundoplication. *Br J Surg* 1998; **85:** 267–71.

20 Martin CJ, Patrikios J, Dent J. Abolition of gas reflux and transient lower esophageal sphincter relaxation by vagal blockade in the dog. *Gastroenterology* 1986; **91:** 890–6.

21 Mittal RK, Holloway R, Dent J. Effect of atropine on the frequency of reflux and transient lower esophageal sphincter relaxation in normal subjects. *Gastroenterology* 1995; **109:** 1547–54.

22 Bais JE, Bartelsman JFWM, Bonjer HJ, Cuesta MA, Go PMHYH, Klinkenberg-Knol EC *et al.* Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355:** 170–4.

23 Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J, Downton J. Control of belching by the lower oesophageal sphincter. *Gut* 1990; **31:** 639–46.

24 Johnsson F, Holloway RH, Ireland AC, Jamieson GG, Dent J. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. *Br J Surg* 1997; **84:** 686–9.

Original article

Validity of surgical simulation for the assessment of operative skill

A. M. Paisley, the late P. J. Baldwin* and S. Paterson-Brown

University Department of Clinical and Surgical Sciences (Surgery), Royal Infirmary and *Working Minds Project, Astley Ainslie Hospital, Edinburgh, UK

Correspondence to: Miss A. M. Paisley, University Department of Surgery, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK (e-mail: anna.paisley@cableinet.co.uk)

Background: Surgical simulators are being promoted as a means of assessing a surgeon's technical skills. Little evidence exists that simulator performance correlates with actual technical ability. This study was undertaken to determine the criterion and construct validity of currently available surgical simulations in the evaluation of technical skill.

Methods: Simulator assessment was carried out on 36 basic surgical trainees, 37 surgically naïve first-year medical students and 16 experienced general surgical consultants. Some 26 trainees and 36 students underwent repeat assessment after 6 months. A previously validated, 19-point technical skill assessment form, based on direct observation of trainee performance in the operating theatre, was also completed by each trainee's supervising consultant.

Results: An insignificant or weak correlation was found between simulator performance and both duration of basic surgical experience and consultant assessment of technical skill. Six months of basic surgical training led to an improvement in performance, not seen in an untrained control group, in only one of the six simulations tested. Discrimination between surgically naïve and experienced subjects was only demonstrated, in part, for four of the six tasks.

Conclusion: The assessment of technical skill needs to be improved. Work is needed to establish the reliability and validity of currently available simulation models before they are formally introduced for high-stakes assessment.

Paper accepted 29 May 2001

British Journal of Surgery 2001, **88**, 1525–1532

Introduction

Although many qualities are needed for a successful surgical career[1,2], technical competence in the operating theatre is vital. Despite its central role in surgical training, the teaching and testing of technical skills has been the least systematic or standardized component of surgical education[3]. The amount of training received in the operating theatre is constantly under threat[4–6]. Considerable concern exists regarding the standard of technical competence in future surgeons and there is a need to ensure accurate assessment of technical progress during training. In the UK, technical skill assessment is deficient[7,8]. While the College examinations tackle factual knowledge of operative technique, they do not satisfactorily test the manual dexterity required to carry out surgical procedures; successful examination candidates have varied practical experience[9–12]. Although all basic surgical trainees (BSTs) must complete a basic surgical skills course, attendance is usually early in training and any assessment is informal and subjective. A higher surgical skills course has recently been introduced for specialist registrars but at present attendance is not mandatory. Logbooks record experience and not expertise. Technical skill accounts for only a single item on both the intercollegiate Basic Surgical Training assessment form and the Higher Surgical Training Record of In-Training Assessment form.

One suggested method of improving technical skill assessment is by the use of surgical simulation[3,13,14]. Simulation can be defined as a device or exercise that enables the participant to reproduce, under test conditions, phenomena that are likely to occur in actual performance[15]. There must be sufficient realism to suspend the disbelief of the participant and to emulate critical aspects of live surgical procedures. To date, simulators have been used for teaching a wide variety of surgical skills[16–19], ranging in sophistication from simple devices that teach knotting and suturing[20–22] to elaborate models simulating actual operative procedures[23–26]. Simulators have been of particular benefit in laparoscopic surgery[27], allowing surgeons to learn and rehearse what are often new skills[28–31]. In recent years, the sophisticated technology of virtual reality, used widely in aviation training, has been adapted for use in surgery[32–36].

It is proposed to introduce simulation into surgical assessment at all levels: to help select candidates on to training programmes, and for assessment of basic trainees as part of the Membership of the Royal College of Surgeons examination, of higher trainees as part of the Certificate of Completion of Surgical Training examination and of consultants as part of revalidation. Simulators are currently being used to assess technical skill in poorly performing surgeons referred to the General Medical Council.

While surgical simulators have been used widely in the teaching environment[16,19], their use in the formal assessment of operative skill is less common and remains controversial. Before surgical simulators are used to assess technical skill formally they must be clearly shown to be reliable (assessments on the same individual are similar under different circumstances) and valid (assessment measures what is intended). To date, limited data exist. While several studies have demonstrated improved simulator performance after training courses using bench models[37,38], few have correlated simulator performance with actual operative ability[30,39]. Some workers have made the assumption that operative ability increases with surgical experience and have attempted to demonstrate that simulator performance discriminates between surgeons at different stages of training. Variable results have been obtained; some groups have shown that simulator performance can discriminate between trainees with differing experience[40–43], but others that it does so inconsistently[29,44], or not at all[34,45–47].

If simulators are valid measures of operative ability, simulator performance should correlate with actual performance in the operating theatre (concurrent validity), should improve with increasing operative experience (senior trainees should score better than juniors), individual trainees should improve over time and it should be possible to discriminate between surgically naïve and experienced subjects (construct validity).

The aim of this study was to determine the concurrent and construct validity of six currently available surgical simulators. The performance of BSTs on each of these simulators was compared with consultant assessment of their technical skill as observed in the operating theatre, with duration of surgical experience, and with performance of surgically naïve medical students and experienced consultant surgeons. It was also determined whether basic surgical training led to an improvement in simulator performance.

Materials and methods

Assessment was carried out on all BSTs on the South-East Scotland Basic Surgical Training scheme between February 1998 and August 1999. At the end of each 6-month speciality attachment the BSTs completed a series of simulated surgical tasks and were evaluated by their supervising consultant using a technical skill assessment form. Seventy-five assessment episodes were carried out on 36 BSTs. Trainee simulator performance was compared with that of 37 first-year medical student volunteers and 16 general surgical consultants. Twenty-six BSTs and 36 students underwent repeat simulator assessment after 6 months. The students did not receive any surgical training in the interval; they were asked only to perform the tasks they could achieve.

Simulation

Simulation assessment was carried out using six, previously described, simulated surgical tasks. All subjects had access to identical instruments and were given uniform verbal instructions. Scoring at all stations was done by a single observer (A.M.P.).

Task 1: knot security

Subjects were asked to tie ten lengths of 2/0 silk (W213; Ethicon, Edinburgh, UK) around a 5-cm diameter horizontal cylinder using three single throws of a single-handed knot. Five ties were performed at surface level and five at depth. After tying each knot, the thread loop around the cylinder was divided at the pole opposite the knot and coded for trainee and depth. Force–extension curves were then produced using an Instron Tensiometer LRX 2KS (Lloyd Instruments, Fareham, UK) and the integrated force of each knot was determined using a method described previously[48].

Task 2: targeted suture placement

Subjects were asked to pass a 2/0 silk suture on a round-bodied needle (W333; Ethicon) through ten pairs of target crosses, at 1·5 cm separation, marked on material held taut within a frame. Wavering of the needle was not allowed; the first attempt at entrance and exit was taken. Each set of targets was coded for trainee and suture deviation from the centre of each target measured by the same single observer, blinded to trainee details, at a later date[41].

Task 3: skin laceration suture

Subjects were asked to suture a 6-cm linear laceration in a simulated skin pad (S301; Ethicon) using simple interrupted sutures and an instrument tying technique[49]. A basic tray and 3/0 monofilament nylon on a reverse cutting needle (W320; Ethicon) were provided[49]. Performance was assessed by time taken and by a task-specific checklist (maximum score 50).

Task 4: small intestinal anastomosis

Subjects were asked to perform an end-to-end anastomosis between two segments of artificial small intestine (203 by 30 mm double-layer bowel; S341; Ethicon) using a single layer of interrupted sero–submucosal sutures (4/0 PDS on a round-bodied needle; W9115T; Ethicon) and hand tying technique[40]. Performance was assessed by time taken and by a task-specific checklist (maximum score 50).

Task 5: standard laparoscopic trainer

Two tasks were performed on a closed box simulator utilizing a single fixed camera port and two operating ports[28]. Time taken and number of errors made were recorded by a single assessor. The first task, adapted from previous work[50], involved the manipulation of Polo® mints (Nestlé Rowntree, York, UK) using two graspers. Leading with the dominant and then non-dominant hand, five mints were transferred from a container to the opposite grasper and placed over five marker pins secured in a cork board. An error was recorded every time a mint was dropped. The second task, previously described by Rosser *et al.*[51], involved uncoiling a 1-m length of cord by transferring successive taped segments (1 cm in length and positioned at 10-cm intervals along the cord) from grasper to grasper. An error was recorded each time the cord was dropped or grasped at a non-taped segment.

Task 6: Minimally Invasive Surgical Trainer – Virtual Reality

Two tasks were carried out on the Minimally Invasive Surgical Trainer – Virtual Reality (MIST-VR) (task 3 and 6), both set to the default parameters agreed by the MIST-VR users' group. Software provided an objective assessment of time taken, number of errors (number of times the instrument moved away from the target) and economy of movement (defined as the ratio of actual path length to ideal path length)[35]. The first task on the MIST-VR tested the subject's ability to acquire and traverse the length of a target object using sequential instrument-to-instrument transfer. The second task tested the subject's ability to acquire a target and apply accurate diathermy to subtargets on its surface while maintaining position at a specified three-dimensional location.

Consultant assessment

A 19-point technical skill assessment form, the reliability and validity of which have been established previously[52], was completed by each BST's supervising consultant, blinded to trainee simulator performance. Form design was based on an anonymous postal survey of all consultant surgeons in south-east Scotland ($n = 111$) which asked for identification and ranking for importance of the skills they expected BSTs to complete after 6 months in their unit[1].

The assessment form asked consultants to select one of four responses for each task. Three of the available responses represented task assessment ('performed task competently', 'performed task but more practice needed' and 'opportunity present but unable to demonstrate task'). If the consultant had not directly observed the trainee performing the task they were asked to select a 'cannot be assessed by me' choice. Each task received a transformed score based on the median weighting of importance awarded to it in the initial survey and the assessment category selected. The 19 scores were then added to generate a single overall score (maximum 123).

Statistical analysis

Non-parametric methods of analysis were used throughout. Spearman's rank correlation was used to test for relationships between simulator performance and both consultant technical skill rating and duration of basic surgical training. Kruskal–Wallis test was used to test for differences in simulator performance between consultant, trainee and student groups. Wilcoxon matched pairs test was used to test for improvement in performance after 6 months. $P < 0.05$ was regarded as significant.

Results

Trainee simulator performance

In all simulated tasks a wide range of trainee performance was observed. In the suture placement task, the total deviation distance ranged from 10 to 50 mm. Time taken to complete the skin laceration suture ranged from 2·5 to 11 min and checklist score from 26 to 48. Time taken to complete the small intestinal anastomosis ranged from 11 to 38 min and checklist score from 10 to 43. The time taken to complete the box trainer tasks ranged from 4 to 18 min and number of errors made from 0 to 48. Time taken to complete the MIST-VR tasks ranged from 2 to 8 min, error score from 2 to 38 and economy score from 12 to 55.

Correlation of trainee simulator performance with consultant technical skill assessment

The percentage scores awarded to trainees by supervising consultants on the technical skills assessment form ranged from –72 to 100 per cent (median 62 per cent). Although the majority of trainees performed well, a small number performed poorly.

There was no significant correlation between BST performance on knotting, suture placement, skin laceration or intestinal anastomosis stations and consultant technical skill score. The only significant correlation between BST laparoscopic performance and consultant technical skill score was with box trainer error (*Table 1*). However, this correlation was weak.

Correlation of simulator performance with duration of surgical experience

There was no significant correlation between BST performance on knotting, suture placement, skin laceration or box trainer stations and duration of BST experience (*Table 2*). A significant negative correlation was found between experience and time taken to complete the small intestinal anastomosis and MIST-VR tasks, but both correlations were weak. There was no significant correlation between duration of experience and box trainer performance or MIST-VR error or economy scores.

Comparison of trainee simulator performance with that of surgically naïve and experienced groups

There was no significant difference between consultant and trainee groups in performance on the knotting station

Table 1 Correlation between simulation performance and consultant technical skill assessment for basic surgical trainees (Spearman's rank correlation)

Simulation	Outcome variable	*P*	rho
Knotting	Integrated force (N): superficial	0·396	0·112
	Integrated force (N): deep	0·385	0·114
Suture placement	Deviation (mm)	0·699	0·051
Skin laceration	Time (s)	0·184	– 0·174
	Checklist score	0·688	0·053
Intestinal anastomosis	Time (s)	0·625	– 0·064
	Checklist score	0·863	0·023
Box trainer	Time (s)	0·081	– 0·227
	Error	0·034	– 0·274
MIST-VR	Time (s)	0·560	– 0·077
	Error	0·194	0·170
	Economy	0·730	– 0·046

MIST-VR, Minimally Invasive Surgical Trainer – Virtual Reality

Table 2 Correlation with duration of basic surgical trainees' experience (Spearman's rank correlation)

Simulation	Outcome variable	*P*	rho
Knotting	Integrated force (N): superficial	0·106	0·188
	Integrated force (N): deep	0·269	0·129
Suture placement	Deviation (mm)	0·835	– 0·025
Skin laceration	Time (s)	0·067	– 0·213
	Checklist score	0·654	0·053
Intestinal anastomosis	Time (s)	0·044	– 0·234
	Checklist score	0·066	0·214
Box trainer	Time (s)	0·053	– 0·224
	Error	0·283	0·126
MIST-VR	Time (s)	0·036	– 0·242
	Error	0·649	– 0·053
	Economy	0·276	– 0·127

MIST-VR, Minimally Invasive Surgical Trainer – Virtual Reality

Table 3 Comparison between consultants, basical surgical trainees and medical students

Simulation	Outcome variable	Consultant	BST	Student	*P*
Knotting	Integrated force (N): superficial	11·5 (10·3–12·8)	11·5 (10·5–12·6)	–	0·953*
	Integrated force (N): deep	10·3 (8·0–12·1)	10·8 (8·7–12·1)	–	0·663*
Suture placement	Deviation (mm)	20·9 (18·1–24·4)	28·3 (23·1–33·8)	38·5 (32·1–47·6)	< 0·001†
Skin laceration	Time (s)	275 (227–370)	304 (247–384)	–	0·230*
	Checklist score	42·5 (40·3–43·8)	38·3 (35·3–40·0)	–	< 0·001*
Intestinal anastomosis	Time (s)	928 (805–1245)	1693 (1326–1899)	–	< 0·001*
	Checklist score	34·0 (32·2–36·3)	31·4 (29·3–34·1)	–	0·014*
Box trainer	Time (s)	392 (342–487)	564 (512–671)	614 (553–769)	< 0·001†
	Error	11·5 (6·0–20·0)	10·5 (7·3–18·0)	13·0 (7·0–17·5)	0·948†
MIST-VR	Time (s)	229 (186–256)	223 (188–292)	248 (205–309)	0·211†
	Error	8·5 (7·9–11·2)	8·5 (6·5–12·0)	9·6 (6·7–13·8)	0·599†
	Economy	20·6 (18·4–22·7)	25·9 (18·9–31·9)	25·1 (21·1–28·8)	0·055†

Values are median (interquartile range). BST, basic surgical trainee; MIST-VR, Minimally Invasive Surgical Trainer – Virtual Reality. *Mann–Whitney *U* test, †Kruskal–Wallis test

(*Table 3*). Consultant deviation distance was significantly less than that of BSTs, which was in turn significantly less than that of students. Consultants attained significantly better checklist scores on the skin laceration suture station than BSTs, and were significantly faster and attained higher checklist scores than BSTs on the small intestinal anastomosis station. Consultants were significantly faster than both BSTs and medical students on the box trainer, but there was no significant difference between BSTs and students. There was no significant difference between the three groups in box trainer error or MIST-VR time, error and economy scores.

Influence of surgical training

In the suture placement station, BSTs, but not students, showed significant improvement in performance after 6 months of training (*Tables 4* and *5*). In the case of small intestinal anastomosis, BSTs were significantly faster after 6 months of training but showed no improvement in checklist score. Unfortunately no control group was available for this station so it is unclear whether this improvement in speed was due to the training received or simply a 'practice effect' from having performed the task previously. No significant difference in BST performance was found after 6 months of training on either the knotting or skin laceration suture stations.

In the case of the laparoscopic tasks, BSTs were significantly faster on both trainers and more efficient on MIST-VR after 6 months of surgical training. However, the medical students also showed significant improvement in these outcome variables, suggesting that this improvement may have been due to a 'practice effect'.

Discussion

If surgical simulators are to be used as valid measures of surgical ability then simulator performance should correlate with performance in the operating theatre (concurrent validity). None of the simulations tested in this study exhibited concurrent validity, as no significant correlation was found between performance on any of the simulators and consultant assessment of technical skill. Determination of such concurrent validity has only been carried out in two previous studies[30,39]. Faulkner *et al.*[39] demonstrated a significant positive correlation between scores achieved by

Table 4 Change in simulator performance over 6 months: basic surgical trainees

Simulation	Outcome variable	0 months	6 months	P^*
Knotting	Integrated force (N): superficial	11·5 (10·9–12·7)	12·3 (10·2–13·2)	0·109
	Integrated force (N): deep	11·0 (8·4–12·1)	11·0 (8·6–12·3)	0·861
Suture placement	Deviation (mm)	30·2 (25·1–34·2)	24·0 (21·7–27·6)	0·002
Skin laceration	Time (s)	317 (262–403)	319 (269–348)	0·322
	Checklist score	38·1 (35·6–40·3)	38·6 (37·2–40·3)	0·741
Intestinal anastomosis	Time (s)	1750 (1307–1940)	1217 (1012–1479)	0·001
	Checklist score	32·6 (29·3–34·8)	33·2 (30·2–37·2)	0·292
Box trainer	Time (s)	585 (527–677)	505 (428–543)	< 0·001
	Error	14·0 (7·8–19·3)	14·0 (9·0–18·0)	0·978
MIST-VR	Time (s)	217 (176–291)	184 (157–215)	0·003
	Error	8·1 (6·0–11·9)	8·7 (6·5–9·9)	0·657
	Economy	26·4 (18·9–32·0)	21·3 (16·4–24·8)	0·002

Values are median (interquartile range). MIST-VR, Minimally Invasive Surgical Trainer – Virtual Reality. *Wilcoxon signed rank test

Table 5 Change in simulator performance over 6 months: medical students

Simulation	Outcome variable	0 months	6 months	P^*
Suture placement	Deviation (mm)	38·2 (31·8–47·3)	35·3 (30·0–47·2)	0·480
Box trainer	Time (s)	620 (563–786)	515 (408–584)	< 0·001
	Error	12·0 (7·0–18·0)	13·0 (7·0–22·0)	0·407
MIST-VR	Time (s)	248 (206–313)	179 (157–222)	< 0·001
	Error	9·5 (6·7–13·4)	7·7 (6·3–10·2)	0·198
	Economy	25·1 (21·4–28·9)	20·1 (17·4–21·9)	< 0·001

Values are median (interquartile range). MIST-VR, Minimally Invasive Surgical Trainer – Virtual Reality. *Wilcoxon signed rank test senior but not junior trainees on a six-station Objective Structured Examination of Technical Skill (OSATS) and faculty rankings of operative ability. Macmillan and Cuschieri[30] showed that overall performance and number of error-free runs, but not time scores, on the Advanced Dundee Endoscopic Psychomotor Tester correlated with consultant assessment of clinical competence. In both these studies assessment of operating ability relied on consultant assessment of trainees who had worked with them up to 2–3 years previously and may not have reflected performance at the time of simulator testing.

If surgical simulators are to be used as valid measures of surgical ability then simulator performance should correlate with trainee experience, should improve with surgical training and should discriminate between surgically naïve and experienced groups (construct validity). Performance on none of the simulations tested in this study correlated strongly with duration of basic surgical training. This was perhaps not surprising as trainees at any level of experience will possess different levels of natural ability. However, performance of individual trainees should improve with surgical training. Such an improvement, in the absence of change in a control group, was found only for the suture placement station.

Discrimination between surgically naïve and experienced groups was possible for suture placement, intestinal anastomosis time and checklist score, skin laceration checklist score and box trainer time. The three groups tested had very disparate surgical capabilities. It is possible that these simulations cannot detect lesser differences in operative skill. As Reznick suggests[53], it may be that simple explanations, such as the ability to handle a needle holder or forceps correctly, are as important as more complex abilities in performing complete surgical tasks.

To date, studies of the ability of simulators to discriminate between subjects at different stages of training have provided equivocal results. Batra *et al.* found that the holding forces of knots tied by medical students were significantly greater than those of knots constructed by emergency physicians or orthopaedic surgeons[45,47]. However, Prystowsky *et al.* found no significant difference between medical students and surgical residents in performance of virtual reality intravenous cannulation[34].

Construct validity has been demonstrated in part by studies that investigated laparoscopic trainers and virtual reality vascular anastomosis, and the OSATS examination system. Derossis *et al.*[29] demonstrated a significant correlation between residency level and score for only four of seven laparoscopic box trainer tasks. A significant difference in performance between laparoscopic and non-laparoscopic surgeons was seen for three tasks only. Vascular surgeons' average performance on a vascular anastomosis virtual reality system was significantly better than that of medical students in only three of eight recorded variables[46]. Martin *et al.* found that global ratings during a six-station OSATS discriminated between resident level, whereas checklists did not; pass/fail scores did not discriminate between residency year in either format[44].

Some groups have shown that simulator performance can discriminate between trainees with differing experience[40–43]. Seki demonstrated that surgeons with more than 6 years' experience placed sutures more accurately than those with less than 1 year's experience[41]. Reznick *et al.* demonstrated that level of training significantly influenced OSATS checklist and global rating scores[40]. MIST-VR has been shown to help laparoscopically naïve subjects overcome the 'fulcrum effect' of the body wall on instrument manipulation[54]. Taffinder *et al.*[42] found significant differences between ten experienced laparoscopic surgeons, ten trainee surgeons and ten non-surgeons in MIST-VR performance. Differences were greatest between consultants and trainees, and consultants and non-surgeons; little difference was seen between trainees and non-surgeons. Chaudhry *et al.*[43] showed that 11 surgeons scored consistently and significantly better on MIST-VR than seven non-surgeons. However, the sample size of the latter study was small and sufficient information was not provided regarding the characteristics of the two groups.

Although surgical simulators have many advantages with regard to surgical training[13], problems remain with current models. The majority of currently available simulators do not allow for objective assessment of performance with 'metrics'. Overall performance is evaluated, most often by time taken, and ergonomic characteristics such as efficiency of movement are not considered. Simulators do not imitate the anatomical variety encountered in surgery, and do not register all of the unpredictable difficulties. If simulations are to fulfil their potential then more realistic models will have to be developed that enable dissection and resection, and that reproduce problems of access. Furthermore, there is debate whether skills acquired in a virtual environment are transferable to the real world.

Acknowledgements

The authors thank the Scottish Council for Postgraduate Medical and Dental Education, the Royal College of Surgeons of Edinburgh and Ethicon UK Ltd who funded the study.

Pamela Baldwin sadly died towards the end of the study and her two co-authors would like to acknowledge her valuable contribution. Her enthusiasm and commitment to the improvement of medical training was unrivalled and she is sorely missed.

References

1 Baldwin PJ, Paisley AM, Brown SP. Consultant surgeons' opinion of the skills required of basic surgical trainees. *Br J Surg* 1999; **86:** 1078–82.

2 Clark CI, Snooks S. Objectives of basic surgical training. *Br J Hosp Med* 1993; **50:** 477–9.

3 Reznick RK. Teaching and testing technical skills. *Am J Surg* 1993; **165:** 358–61.

4 Department of Health. *Hospital Doctors: Training for the future. The Report of the Working Group on Specialist Medical Training.* London: HMSO, 1993.

5 NHS Management Executive. *Junior Doctors, the 'New Deal'. Working Arrangements for Hospital Doctors and Dentists in Training.* London: NHS Management Executive, 1991.

6 Beecham L. New Scottish CMO criticises training reforms. *BMJ* 1996; **313:** 947.

7 Pietroni M. The assessment of competence in surgical trainees. *Ann R Coll Surg Engl* 1993; 75(Suppl 6): 200–2.

8 Pollock AV. How do we measure surgical competence? *Eur J Surg* 1996; **162:** 355–60.

9 Borlase BC, Bartle EJ, Moore EE. Does the in-service training examination correlate with clinical performance in surgery? *Curr Surg* 1985; **42:** 290–2.

10 Lazar HL, DeLand EC, Tompkins RK. Clinical performance *versus* in-training examinations as measures of surgical competence. *Surgery* 1980; **87:** 357–62.

11 Schwartz R, Donnelly M, Drake D, Sloan D. Faculty sensitivity in detecting medical student's clinical competence. *Clin Invest Med* 1993; **16**(Suppl B): 87.

12 Kopta JA. An approach to the evaluation of operative skills. *Surgery* 1971; **70:** 297–303.

13 MacIntyre IM, Munro A. Simulation in surgical training. *BMJ* 1990; **300:** 1088–9.

14 Barnes RW. Surgical handicraft: teaching and learning surgical skills. *Am J Surg* 1987; **153:** 422–7.

15 Krummel TM. Surgical simulation and virtual reality: the coming revolution. *Ann Surg* 1998; **228:** 635–7.

16 Anonymous. The craft of surgery. The anastomosis workshop, March 1981. *Ann R Coll Surg Engl* 1981; **63:** 405–10.

17 Hamdorf JM, Hall JC. Acquiring surgical skills. *Br J Surg* 2000; **87:** 28–37.

18 Allen PI. Anastomosis: a craft workshop for surgical trainees. *Aust N Z J Surg* 1990; **60:** 943–5.

19 Barnes RW, Lang NP, Whiteside MF. Haltsedian technique revisited. Innovations in teaching surgical skills. *Ann Surg* 1989; **210:** 118–21.

20 Boyle DE, Gius JA. Tie and suture training board. *Surgery* 1968; **63:** 434–6.

21 Munro A, Park KG, Atkinson D, Day RP, Capperauld I. Skin simulation for minor surgical procedures. *J R Coll Surg Edinb* 1994; **39:** 174–6.

22 Thomas WE, Lee PW, Sunderland GT, Day RP. A preliminary evaluation of an innovative synthetic soft tissue simulation module ('Skilltray') for use in basic surgical skills workshops. *Ann R Coll Surg Engl* 1996; **78**(Suppl 6): 268–71.

23 Jones RT, Thomson JP. A stoma jig for surgical craft workshops. *Ann R Coll Surg Engl* 1988; **70:** 311–12.

24 Stotter AT, Becket AJ, Hansen JP, Capperauld I, Dudley HA. Simulation in surgical training using freeze dried material. *Br J Surg* 1986; **73:** 52–4.

25 Greenhalgh RM, Eastcott HH, Mansfield AO, Taylor DE. Aneurysm jig for anastomosis technique. *Ann R Coll Surg Engl* 1987; **69:** 199–200.

26 Apley AG. Fixation of fractures: organising a course. *Ann R Coll Surg Engl* 1980; **62:** 219–22.

27 Jakimowicz JJ. The European Association for Endoscopic Surgery recommendations for training in laparoscopic surgery. *Ann Chir Gynaecol* 1994; **83:** 137–41.

28 Munro A, Park KG, Atkinson D, Day RP, Capperauld I. A laparoscopic surgical simulator. *J R Coll Surg Edinb* 1994; **39:** 176–7.

29 Derossis AM, Fried GM, Abrahamowicz M, Sigman HH, Barkun JS, Meakins JL. Development of a model for training and evaluation of laparoscopic skills. *Am J Surg* 1998; **175:** 482–7.

30 Macmillan AI, Cuschieri A. Assessment of innate ability and skills for endoscopic manipulations by the Advanced Dundee Endoscopic Psychomotor Tester: predictive and concurrent validity. *Am J Surg* 1999; **177:** 274–7.

31 Taffinder N, Smith SG, Huber J, Russell RC, Darzi A. The effect of a second-generation 3D endoscope on the laparoscopic precision of novices and experienced surgeons. *Surg Endosc* 1999; **13:** 1087–92.

32 Satava RM. Virtual reality surgical simulator. The first steps. *Surg Endosc* 1993; **7:** 203–5.

33 Ota D, Loftin B, Saito T, Lea R, Keller J. Virtual reality in surgical education. *Comp Biol Med* 1995; **25:** 127–37.

34 Prystowsky JB, Regehr G, Rogers DA, Loan JP, Hiemenz LL, Smith KM. A virtual reality module for intravenous catheter placement. *Am J Surg* 1999; **177:** 171–5.

35 Wilson MS, Middlebrook A, Sutton C, Stone R, McCloy RF. MIST VR: a virtual reality trainer for laparoscopic surgery assesses performance. *Ann R Coll Surg Engl* 1997; **79:** 403–4.

36 Ziegler R, Fischer G, Muller W, Gobel M. Virtual reality arthroscopy training simulator. *Comput Biol Med* 1995; **25:** 193–203.

37 Saifi J, Chang BB, Paty PSK, Kaufman J, Leather RP, Shah DM. An animal model for instructing and the study of *in situ* arterial bypass. *J Vasc Surg* 1990; **12:** 538–40.

38 Taffinder N, Sutton C, Fishwick RJ, McManus IC, Darzi A. Validation of virtual reality to teach and assess psychomotor skills in laparoscopic surgery. In: Westwood JD,

Hoffman HM, Stredney D, Weghorst SJ, eds. *Medicine Meets Virtual Reality.* Washington, DC: IOS Press, 1998: 124–30.

39 Faulkner H, Regehr G, Martin J, Reznick R. Validation of an objective structured assessment of technical skill for surgical residents. *Acad Med* 1996; **71:** 1363–5.

40 Reznick R, Regehr G, MacRae H, Martin J, McCulloch W. Testing technical skill via an innovative 'bench station' examination. *Am J Surg* 1997; **173:** 226–30.

41 Seki S. Accuracy of suture placement. *Br J Surg* 1987; **74:** 195–7.

42 Taffinder NJ, Russell RCG, McManus IC, Jansen J, Darzi A. An objective assessment of surgeons' psychomotor skills: validation of the MIST-VR laparoscopic simulator. *Br J Surg* 1998; **85**(Suppl 1): 75 (Abstract).

43 Chaudhry A, Sutton C, Wood J, Stone R, McCloy R. Learning rate for laparoscopic surgical skills on MIST VR, a virtual reality simulator: quality of human–computer interface. *Ann R Coll Surg Engl* 1999; **81:** 281–6.

44 Martin JA, Regehr G, Reznick R, MacRae H, Murnaghan J, Hutchison C *et al.* Objective structured assessment of technical skill (OSATS) for surgical residents. *Br J Surg* 1997; **84:** 273–8.

45 Batra EK, Taylor PT, Franz DA, Towler MA, Edlich RF. A portable tensiometer for assessing surgeon's knot tying technique. *Gynecol Oncol* 1993; **48:** 114–18.

46 O'Toole RV, Playter RR, Krummel TM, Blank WC, Cornelius NH, Roberts WR *et al.* Measuring and developing suturing technique with a virtual reality surgical simulator. *J Am Coll Surg* 1999; **189:** 114–27.

47 Batra EK, Franz DA, Towler MA, Rodeheaver GT, Thacker JG, Zimmer CA *et al.* Influence of emergency physician's tying technique on knot security. *J Emerg Med* 1992; **10:** 309–16.

48 Hanna GB, Frank TG, Cuschieri A. Objective assessment of endoscopic knot quality. *Am J Surg* 1997; **174:** 410–13.

49 O'Connor HM, McGraw RC. Clinical skills training: developing objective assessment instruments. *Med Educ* 1997; **31:** 359–63.

50 Steele RJ, Hosking SW, Chung SC. Graded exercises for basic training in laparoscopic surgery. *J R Coll Surg Edinb* 1994; **39:** 112–16.

51 Rosser JC, Rosser LE, Savalgi RS. Skill acquisition and assessment for laparoscopic surgery. *Arch Surg* 1997; **132:** 200–4.

52 Paisley AM, Baldwin PJ, Paterson-Brown S. Feasibility, reliability and validity of a new assessment form for use with basic surgical trainees. *Am J Surg* 2001; **182:** 20–2.

53 Reznick RK. Virtual reality surgical simulators: feasible but valid? *J Am Coll Surg* 1999; **189:** 127–8.

54 Gallagher AG, McClure N, McGuigan J, Crothers I, Browning J. Virtual reality training in laparoscopic surgery: a preliminary assessment of minimally invasive surgical trainer virtual reality (MIST VR). *Endoscopy* 1999; **31:** 310–13.

Original article

'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery

C. P. Delaney, V. W. Fazio, A. J. Senagore, B. Robinson, A. L. Halverson and F. H. Remzi

Department of Colorectal Surgery/A-111, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA
Correspondence to: Dr C. P Delaney (e-mail delanec@ccf.org)

Background: A combination of factors has emphasized the need to reduce postoperative stay after surgery. Multimodal care plans may shorten hospital stay, but have been associated with high readmission rates and are generally reserved for straightforward, non-complicated colonic (not rectal) resections. This study evaluated a 'fast track' protocol in patients undergoing major colonic and rectal surgery.

Methods: Sixty consecutive patients (median age 44·5 (range 13–70) years) underwent major procedures over a 6-week period on one colorectal service. Nasogastric tubes and epidural anaesthesia were not used. Patients participated in a protocol of early diet and early ambulation, and were discharged after meeting defined criteria.

Results: Fifty-eight patients (97 per cent) were deemed suitable for the 'fast track' approach at the time of surgery and stayed for a mean(s.d.) of 4·3(1·6) days after operation. Patients in diagnosis-related group (DRG) 148 (colorectal resection with co-morbidity; $n = 40$) stayed for 4·6(1·7) days, which was longer than those in DRG 149 (without co-morbidity; $n = 18$) who stayed 3·5(0·8) days ($P = 0{\cdot}01$). Three patients (5 per cent) required a nasogastric tube for vomiting. There were no readmissions directly attributable to 'fast track' failure, although four patients (7 per cent) were readmitted within 30 days of operation for other reasons. Eight poorly compliant patients stayed for 5·1(1·1) days ($P = 0{\cdot}02$ *versus* compliant patients). 'Fast track' patients had a shorter length of stay than patients receiving traditional care on other colorectal services during the same time period (compared by DRG 148, DRG 149 and for all patients) ($P < 0{\cdot}0001$).

Conclusion: The 'fast track' protocol allows patients with high levels of co-morbidity undergoing complex colorectal and reoperative pelvic surgery to benefit from a rapid recovery and early discharge from hospital. The approach is safe and has low readmission rates.

Paper accepted 26 June 2001

British Journal of Surgery 2001, 88, 1533–1538

Introduction

The traditional postoperative stay in hospital after major gastrointestinal surgery has been between 5 and 10 days, with an approximate median stay of 7 days[1,2]. Some recent large studies suggest that stay is even longer[3]. Over the past decade, advances in healthcare and an increased understanding of postoperative physiology have led to a trend towards a shorter hospital stay after operation[4,5]. This philosophy has been driven by the hope of increasing utilization of available hospital beds, as well as reductions in healthcare expenditure.

Factors that delay discharge from hospital after laparotomy include pain, nausea and vomiting, persistence of ileus, fatigue, mechanical factors (such as the presence of drains) and stress-induced organ dysfunction[6]. By addressing these factors with a multimodal rehabilitation programme, involving a highly scripted preoperative and postoperative care plan which regulates the introduction of analgesia, diet and ambulation, Kehlet and Mogensen[7] have described a median postoperative stay of 2 days in 18 patients undergoing elective sigmoid colectomy. The safety of this approach has been supported by the advent of laparoscopy which has spurred open studies confirming that patients can undergo major intestinal surgery, eat on the first postoperative day and be discharged as early as 48 h after operation, without adverse effects[8–11].

Several authors have described multimodal care plans, although without the pre-emptive epidurals, oral cathartics and prokinetic agents used by Kehlet and colleagues. Implementation of such plans can reduce hospital stay[5,12,14] and perhaps the cost of hospitalization[15], but these plans have been associated with relatively high readmission rates and have sometimes discharged patients on liquid diets to reduce the time spent in hospital[14]. Furthermore, these pathways have generally been reserved for patients undergoing relatively straightforward, non-complicated colonic resection, but not rectal resection or major pelvic surgery.

This paper addresses the hypothesis that a multimodal care plan can be applied to patients undergoing major abdominal and pelvic colorectal surgery, who have significant co-morbid diseases and who may have undergone previous major abdominal surgery. Success of the 'fast track' protocol was judged on the basis of early discharge, without evidence of an increase in morbidity or readmission rates.

Patients and methods

After approval from the institutional review board, 60 consecutive patients were scheduled for elective laparotomy and intestinal resection on one colorectal service over a 6-week period. Elective patients were defined as those admitted on the day of surgery for a routinely planned operation on a non-urgent basis. Patients undergoing rectal or pelvic surgery, or reoperation, and patients with co-morbidities were included. Less major procedures, such as ventral hernia repair and loop ileostomy closure, were not included.

Two patients were excluded from the 'fast track' protocol at the time of surgery. One patient was unsuitable because of a planned early (day 5) second-stage Turnbull Cutait procedure, when delayed amputation of the pull-through rectal stump was performed. A second patient deemed unsuitable for the protocol was kept on parenteral nutrition for 5 days after combined gastric, duodenal, small bowel and multiple-site colonic surgery for recurrent fistulating Crohn's disease. This left 58 patients for postoperative rehabilitation using the 'fast track' protocol.

The principle of the 'fast track' care pathway was explained to each patient at the time a decision was made for surgery. Patients were seen once before operation as outpatients by the colorectal nurse manager and given a patient information sheet indicating the expected postoperative course of recovery and rehabilitation. Patients were admitted to hospital 2 h before surgery. Intravenous patient-controlled analgesia (PCA) systems were used for all patients. Epidurals were not used during or after surgery. Orogastric tubes were placed after induction of anaesthesia and removed before endotracheal extubation. Patients were permitted to walk on the evening of surgery if desired, and were offered liquids as desired. Analgesia was supplemented with intravenous ketorolac 30 mg every 6 h if needed. On day 1 after operation patients were actively encouraged to walk at least one circuit of the nursing floor (approximately 60 m) up to five times, to sit out of bed between walks, and to do regular incentive spirometry. They were allowed non-carbonated liquids *ad libitum*, and were offered solid food that evening if able to tolerate oral fluids. Oral analgesia was started on day 2 after operation, if liquid or diet was being tolerated, and the PCA was discontinued. The catheter was removed from the bladder on day 2; intra-abdominal suction drains were also removed unless there was a specific concern requiring them to be left in place. Stoma care instruction was commenced by dedicated enterostomal therapy nurses on the day after operation, and patients had between two and four daily lessons before discharge. The nurse : patient ratio on the colorectal wards was approximately 1 : 4.

Patients were discharged once they had passed either flatus or stool, were able to drink and eat solid food comfortably, and were comfortable on oral analgesia. If the patient was not happy with the discharge plans, they were kept for an additional 12–24 h until fully reassured. Patients who lived more than 100–150 miles from the hospital were encouraged to stay in a hotel or guest house within the area of the hospital for 1–3 further days. No patient received home visits from a physician.

All complications were determined prospectively at the time of discharge and were reassessed by telephone follow-up or at an outpatient visit, up to a minimum of 30 days after operation. Patients were prospectively designated poorly compliant for the purpose of *post hoc* analysis if they did not follow reasonable encouragement by the medical and nursing staff about diet, ambulation or incentive spirometry, or if they stayed in hospital for longer than the interval defined by the above criteria and it was deemed unnecessary medically by the medical staff.

Results are presented as mean(s.d.) for parametric and median (range) for non-parametric continuous variables, and as frequencies and percentages for categorical variables. Statistical analysis was performed using StatView for Windows version 5.0.1 (SAS Institute, Cary, North Carolina, USA). Continuous variables were examined using the Kolmogorov–Smirnov test for measurement of normality. Normally distributed data were compared using Student's t test, and the Mann–Whitney U test was used for non-parametric data. The χ^2 test was used for non-continuous variables. Data were analysed on an intention-to-treat basis, accepting $P < 0{\cdot}05$ as significant, and were also analysed on the basis of compliance with the protocol. Study results were compared with available data from this institution for length of stay, grouped by staff surgeon within the Department of Colorectal Surgery, and by hospital-coded diagnosis-related group (DRG), a standard national classification system in this country[16,17]. Using this system, DRG 148 is classified as major small and large bowel surgery with co-morbidity (a pre-existing condition that increases length of stay by 1 day in 75 per cent of cases) or complication (a complication that increases length of stay by 1 day in 75 per cent of cases), and DRG 149 as without co-morbidity or complication.

Results

Fifty-eight (97 per cent) of 60 potential patients were enrolled over a 6-week period. The mean(s.d.) age was 44·4(13·5) (median 44·5 (range 13–70)) years and 22 patients (38 per cent) were female. Patients were stratified by American Society of Anesthesiologists (ASA) classification into: ASA I, one patient (2 per cent); ASA II, 34 patients (59 per cent); ASA III, 22 patients (38 per cent); and ASA IV, one patient (2 per cent). Thirty-four patients (59 per cent) had undergone one or more previous major laparotomies, two (3 per cent) had undergone minor laparotomies (appendicectomy and cholecystectomy) and 22 (38 per cent) had never had a laparotomy. Forty patients were classified as DRG 148, while 18 were classified as DRG 149. Indications for surgery are given in *Table 1*. Some 36 patients had other co-morbidities: there were seven patients with hypertension, three with previous myocardial infarction or congestive cardiac failure, one had previously had a stroke, four had chronic obstructive airway disease, two were morbidly obese, five had cirrhosis or hepatitis, four had diabetes mellitus, ten were steroid dependent, one was hypothyroid, two were receiving total parenteral nutrition, three had malnutrition, two had short bowel syndrome, two were narcotic addicts, one had thromboembolic disease, one had necrotizing pancreatitis, six had peptic ulcer disease or gastro-oesophageal reflux, four had a ventral hernia and six had other co-morbidities.

Thirty-nine patients were operated on for inflammatory bowel disease, 15 had primary or recurrent colorectal cancer and six had other indications (*Table 1*). The resections and types of reconstruction for the patients are indicated in *Table 1*. Median time from initiation of anaesthesia to extubation was 180 (range 98–262) min. Median blood loss was 300 (0–725) ml.

Patients who were classified into DRG 148 ($n = 40$) stayed 4·6(1·7) days, significantly longer than those in DRG 149 ($n = 18$) who stayed only 3·5(0·8) days ($P = 0{\cdot}01$). Five patients had a nasogastric tube left in place in error until the morning after surgery. One patient had a nasogastric tube left in place for 48 h. This was initially left in place in error, and drained 2500 ml in the 48 h before being removed. Patients who were given a nasogastric tube in error stayed 4·5(1·6) days compared with 4·2(1·6) days for those without a nasogastric tube ($P = 0{\cdot}7$). The presence of a defunctioning loop ileostomy (4·5(1·7) days without *versus* 3·9(1·1) days with ileostomy; $P = 0{\cdot}16$) or a history of previous abdominal surgery (4·1(1·2) days without *versus* 4·4(1·7) days with previous surgery; $P = 0{\cdot}4$) did not affect time to discharge. Patients who had either an end or loop stoma stayed for

Table 1 Diagnosis, resection performed at laparotomy and reconstruction performed for 58 patients who were treated according to the 'fast track' protocol during recovery after laparotomy

Diagnosis	*n*	Resection performed	*n*	Reconstruction performed	*n*
Ulcerative colitis	26	None*	3	Ileal pouch–anal anastomosis	18
Ulcerative colitis with cancer	2	Proctocolectomy	17	Kock pouch (primary or re-do)	6
Crohn's disease	10	Proctectomy	8	Colorectal anastomosis	5
Colorectal cancer	11	Colectomy	10	Colo(± pouch)–anal anastomosis	3
Recurrent colorectal cancer	2	Ileoanal pouch excision or mobilization	6	Ileocolic anastomosis	11
Enterocutaneous fistula	3	Abdominoperineal resection of rectum or ileoanal pouch	4	Small bowel anastomosis (single or multiple)	3
Diverticular disease	2	Ileocolic resection	9	Strictureplasty (single or multiple)	5
Hirschsprung's disease	1	Small bowel resection	4	End ileostomy/colostomy	12
Pancreaticocolic fistula	1	Reversal of Hartmann's procedure	1	Defunctioning loop ileostomy	22
Total	58	Total	62	Total	85

*One patient underwent laparotomy, lysis of adhesions and multiple strictureplasties for recurrent Crohn's disease; two patients underwent laparotomy, lysis of adhesions and revision of Kock pouches, without pouch resection

Table 2 Complications in 12 of the 58 patients managed after operation using the 'fast track' pathway, subdivided by diagnosis-related group, compliance and whether patients were managed on the specialist colorectal nursing floor

	All (*n* = 58)	DRG 148 (*n* = 40)	Poor compliers (*n* = 8)	Non-colorectal nursing (*n* = 16)
Total complications	21	20†	2	7
Patients with complications	12	12‡	2	5
Nasogastric tube reinsertion	3	3	0	0
Readmission	4	4	1	2
Ileus or partial small bowel obstruction	7	1	1	2
Chest				
Atelectasis	1	1	0	1
Pneumonia	1*	1	0	0
Venous thrombosis	2	2	0	1
Wound infection or abdominal abscess	2	2	0	1
Other	1	1	0	0

*Nasogastric tube in error. DRG, diagnosis-related group. †$P < 0·001$, ‡$P < 0·01$ *versus* DRG 149 (χ^2 test)

4·0(1·1) days, in contrast to those without a stoma who stayed for 4·8(2·1) days ($P = 0·06$). Eighteen patients undergoing either proctocolectomy or proctectomy and ileal pouch–anal anastomosis stayed for 3·6(1·0) days.

Time to discharge from hospital was significantly delayed in the eight patients who showed poor compliance with the 'fast track' protocol (from 4·3(1·6) days in all patients to 5·1(1·1) days in poor compliers; $P = 0·02$). There was no significant difference in the volume of fluids ingested while in hospital between those who followed the 'fast track' protocol and those who complied poorly (four of whom were ASA II and four ASA III), or those who developed complications (734(507) ml for all patients at day 1 and 1036(597) ml for all patients at day 3). Equally, there was no difference in ambulation between groups (2·0(2·0) walks for all patients at day 1, 3·8(1·6) walks for all patients at day 3). Oral pain medication was commenced at the same time as discontinuation of PCA, at 2·0(0·7) (median 2·0) days after operation.

Four patients (7 per cent) were readmitted to hospital within 30 days of operation. No readmissions were related to ileus or abdominal wound pain, as might have been expected with a failure of the 'fast track' approach. Two patients (3 per cent) were readmitted for heparinization for deep venous thrombosis. One patient (after abdominoperineal resection) was readmitted on day 10 for increasing perineal pain and concern about a pelvic abscess; investigations were negative. One patient was admitted to another institution for computed tomography-guided drainage of an intra-abdominal abscess. Twelve patients (21 per cent) developed the complications described in *Table 2*, and had a delayed discharge to 5·5(2·4) days ($P = 0·04$ *versus* no complications). Sixteen patients who were not managed on the specialist colorectal nursing floor owing to bed constraints had similar operations to the remaining 42. There was no difference in time to discharge or complication rate between patients managed on colorectal or non-colorectal nursing floors (*Table 2*).

Thirty-five patients (60 per cent) were discharged home. Twenty-three patients stayed in a local hotel for 2–3 days before returning home. Patients discharged home stayed for 4·3(1·6) days in hospital, while patients discharged to a hotel stayed 4·3(1·5) days. No patient required regular home nursing care or was admitted to a non-hospital-based nursing care facility.

Evaluation of historical length of stay at this institution for patients in DRG 148 and 149 has shown a slight reduction for the year 1999, compared with the decade from 1991 to 1999 (*Table 3*). The 'fast track' protocol has been employed since the completion of this study in March 2000, and only the service using the 'fast track' approach has shown a reduction in length of stay for the year 2000 to the end of June. Furthermore, this reduction in length of stay appears to have been well maintained since completion of the study, as mean length of stay for DRG 148 and DRG 149 was 4·7 days from March to June 2000 inclusive, with a highly significant reduction in length of stay for DRG 148, DRG 149 and for patients overall (DRG 148 and DRG 149 combined) (*Table 3*).

Discussion

This study addressed the hypothesis that a 'fast track' care pathway can be applied to patients undergoing major abdominal and pelvic colorectal surgery. A cohort of patients undergoing complex intestinal surgery was studied, who had significant co-morbid disease, many with a history of major abdominal surgery. Based on the pre-

Table 3 Data from the institutional database on length of stay, comparing the service in which the 'fast track' protocol was adopted with the remaining colorectal services

	1991–1999		1999		March to June 2000	
	n	Stay (days)*	*n*	Stay (days)*	*n*	Stay (days)*
DRG 148						
Study service (V.W.F.)	1784	9·5	185	8·6	62	5·7†
Other CRS services	6459	9·8	824	8·8	162	10·1
DRG 149						
Study service (V.W.F.)	742	6·4	69	5·2	44	3·5‡
Other CRS services	2256	6·4	327	5·1	111	4·5
DRG 148 and DRG 149						
Study service (V.W.F.)	2526	8·6	254	7·7	106	4·7†
Other CRS services	8715	8·9	1151	7·7	273	7·7

The 'fast track' study was implemented in March 2000 and figures are shown for March to June (currently available data). *Mean length of stay. DRG, diagnosis-related group; CRS, colorectal surgery. †$P < 0{\cdot}0001$, ‡$P = 0{\cdot}002$ *versus* other services (Student's *t* test)

defined criterion of success as early discharge without an associated increase in morbidity or readmission rates, the pathway appears to have been successful, although it must be noted that the median age in this cohort was 44·5 years. The results support the practice of extending multimodal care pathways to patients with co-morbidity undergoing major reoperative abdominal and pelvic surgery.

The results of this study raise important points about the success or failure of such clinical pathways. The 'fast track' approach is applicable to the majority of patients undergoing surgery; unless patients have a physical disability precluding early ambulation they should be encouraged to be active early after operation. In contrast to the findings of Basse *et al.*[18], the present study found that patients without co-morbidity (DRG 149) did better than those with co-morbidity, and had a hospital stay of only 3·5(0·8) days. A history of previous abdominal surgery did not hinder early recovery. The results of this study demonstrate that clinical pathways can be successful in a large group of patients undergoing complex reoperative abdominal and pelvic surgery, attested to by the mean stay of 3·6 days in patients undergoing ileal pouch–anal anastomosis. These results support the findings of other authors[5,12,13] and suggest that a short stay may be achieved without the use of thoracic epidural catheters.

The real success of this approach to postoperative care is the eagerness with which patients embraced the 'fast track' approach. Patients appeared to have significantly less pain, used fewer opiates, and returned to normal physical activities in a much shorter time than patients managed with traditional techniques. Although epidural anaesthesia was not used, these patients had a rapid recovery after major intestinal surgery. This recovery was similar to that described by Basse *et al.*[18], who reported on 60 patients with a median stay of 2 days, 32 of whom were discharged within 48 h of surgery, for a mean stay of 4·0 days. In the present report, patients without major co-morbidity who underwent major colonic and rectal resections stayed only 3·5(0·8) days in hospital. This length of stay was not influenced by the presence of a defunctioning loop ileostomy, although a loop ileostomy might be expected to reduce time to recovery from ileus as the patient does not have to wait for the colon to recover.

The psychological attitude of the patient is important. Patients who did not comply with the suggestions of the medical team stayed significantly longer (5·1(1·1) days). This problem may be addressed by managing these patients on a specialized nursing floor with a standard nursing approach, even though the data in this paper did not show a difference in results between nursing floors.

In this group of patients, there were no direct failures of the 'fast track' approach. Nobody was admitted with symptoms of nausea, vomiting or abdominal distension. There were no deaths and no anastomotic leaks. One of the main concerns with early discharge after major reconstructive abdominal surgery is that patients may suffer an anastomotic complication at home. Published experience suggests that anastomotic leaks occur rarely in patients who follow a clinical pathway[5,6,12,13,18]. Furthermore, to date there have been no adverse effects reported when patients have been instructed to call the physician if they develop suspicious symptoms at home[18]. This issue warrants careful consideration in future studies.

It has been argued that discharging patients earlier will provide only marginal benefits in terms of cost savings, as the days close to discharge are not expensive on resources[19]. Apart from the benefits to the patient of early discharge, this opinion does not recognize the reduction in overall costs to the institution from early discharge (R. P. Billingham, personal communication)[15]. Another benefit of early discharge is vacation of a hospital bed, allowing another patient to be treated in an era when the number of hospital beds has been drastically reduced. This helps to reduce waiting lists and decreases institutional costs by improving efficiency[20].

These preliminary data permit several conclusions: first, that application of a 'fast track' protocol is feasible for patients with high levels of co-morbidity undergoing complex colorectal and reoperative pelvic surgery; second, that the protocol permits rapid recovery and a short hospital stay; and third, that there appear to be no adverse events related to the accelerated nature of the postoperative care. The approach may allow patients to be discharged significantly earlier from hospital, thereby reducing rates of nosocomial infection, allowing more efficient use of hospital beds and reducing hospital costs. A randomized prospective trial is currently under way to answer remaining questions about the safety, applicability and patient acceptability of such 'fast track' care protocols.

Acknowledgements

C. P. Delaney was the 1999–2000 Surgical Travelling Fellow of the Royal College of Surgeons in Ireland.

References

1 Schoetz DJJ, Bockler M, Rosenblatt MS, Malhotra S, Roberts PL, Murray JJ *et al.* 'Ideal' length of stay afer colectomy: whose ideal? *Dis Colon Rectum* 1997; **40:** 806–10.

2 Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D *et al.* Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum* 1995; **38:** 480–7.

3 Retchin SM, Pinberthy L, Desch C, Brown R, Jerome-D'Emilia B, Clement D. Perioperative management of colonic cancer under Medicare risk programs. *Arch Intern Med* 1997; **157:** 1878–84.

4 Pearson SD, Goulart-Fisher D, Lee TH. Critical pathways as a strategy for improving patient care: problems and potential. *Ann Intern Med* 1995; **123:** 941–8.

5 Archer SB, Burnett RJ, Flesch LV, Hobler SC, Bower RH, Nussbaum MS *et al.* Implementation of a clinical pathway decreases length of stay and hospital charges for patients undergoing total colectomy and ileal pouch/anal anastomosis. *Surgery* 1997; **122:** 699–705.

6 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78:** 606–17.

7 Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999; **86:** 227–30.

8 McClane S, Senagore A, Marcello P. Experience-based postoperative care in laparoscopic-assisted colectomy reduces length of stay. *Dis Colon Rectum* 2000; **43:** A54 (Abstract).

9 Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. *Lancet* 1995; **345:** 763–4.

10 Binderow SR, Cohen SM, Wexner SD, Nogueras JJ. Must early postoperative oral intake be limited to laparoscopy? *Dis Colon Rectum* 1994; **37:** 584–9.

11 Reissman P, Teoh T-A, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* 1995; **222:** 73–7.

12 Di Fronzo LA, Cymerman J, O'Connell TX. Factors affecting early postoperative feeding following elective open colon resection. *Arch Surg* 1999; **134:** 941–6.

13 Bradshaw BCG, Liu SS, Thirlby RC. Standardized perioperative care protocols and reduced length of stay after colon surgery. *J Am Coll Surg* 1998; **186:** 501–6.

14 Behrns KE, Kircher AP, Galanko JA, Brownstein MR, Koruda MJ. Prospective randomized trial of early initiation and hospital discharge on a liquid diet following elective intestinal surgery. *J Gastrointest Surg* 2000; **4:** 217–21.

15 Pritts TA, Nussbaum NS, Flesch LV, Fegelman EJ, Parikh AA, Fischer JE. Implementation of a clinical pathway decreases length of stay and cost for bowel resection. *Ann Surg* 1999; **230:** 728–33.

16 Munoz E, Goldstein J, Lory MH, Brewster JG, Johnson H, Kahn BA *et al.* The DRG hospital payment system, surgical readmissions and cost containment. *Am Surg* 1990; **56:** 683–7.

17 Rhodes RS, Sharkey PD, Horn SD. Effect of patient factors on hospital costs for major bowel surgery: implications for managed health care. *Surgery* 1995; **117:** 443–50.

18 Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232:** 51–7.

19 Taheri PA, Butz DA, Greenfield LJ. Length of stay has minimal impact on the cost of hospital admission. *J Am Coll Surg* 2000; **191:** 123–30.

20 Taheri PA, Butz DA, Greenfield LJ. Academic health systems management: the rationale behind capitated contracts. *Ann Surg* 2000; **231:** 849–59.

Original article

Conservative management of appendix mass in children

J. Gillick*, M. Velayudham† and P. Puri*†‡

*The Chidren's Research Centre, Our Lady's Hospital for Sick Children, ‡The Children's Hospital and the †National Children's Hospital, Dublin, Ireland

Correspondence to: Mr P. Puri, The Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland (e-mail: ppuri@crumlin.ucd.ie)

Background: The management of an appendix mass in children is controversial. An experience of conservative management of appendix masses in a paediatric population over the last 19 years is reviewed.

Methods: The medical records of all children who presented with an appendix mass to one of three children's hospitals between 1982 and 2000 were reviewed. In that interval 427 children with a mean age of 7·3 years (range from 2 months to 18 years) presented with an appendix mass. Sixteen children had an immediate appendicectomy. The remaining 411 children were treated conservatively by close observation and antibiotics, with intravenous fluids and nasogastric suction if required. Once the child was well enough for discharge home, elective appendicectomy was booked for 4–6 weeks later.

Results: Three hundred and forty-six (84·2 per cent) of the children responded to initial conservative management and were discharged after a median stay of 6 (range 3–24) days. The children returned 4–6 weeks later for elective appendicectomy. The complication rate for elective appendicectomy was 2·3 per cent (eight patients). Those who had an uncomplicated elective appendicectomy had a median hospital stay of 3 (range 1–6) days. Histological examination demonstrated acute or subacute inflammation in 50·8 per cent of appendices removed at elective appendicectomy.

Conclusion: Non-operative management of an appendix mass followed by elective appendicectomy is a safe and effective method of management.

Paper accepted 1 July 2001

British Journal of Surgery 2001, **88**, 1539–1542

Introduction

Appendicitis is the most common surgical emergency in paediatric practice. In this hospital a diagnosis of appendicitis is made in approximately 40 per cent of children who present with acute abdominal pain to the accident and emergency department.

An appendix mass results from appendicitis that is localized by oedematous, adherent omentum and loops of small bowel[1]. In contrast, an appendix abscess is a localized suppurative process that may occur at any time in the course of appendicitis, or may complicate an appendix mass. An appendix mass is discovered at the time of presentation in about 10 per cent of children with appendicitis[2]. The incidence is higher during the first 3 years of life, when one-third of patients with appendicitis have been reported to present with an appendix mass[1].

The management of an appendix mass in children is controversial. Many authors recommend non-operative management with antibiotics, followed by delayed appendicectomy, as the treatment of choice[2–4]. Others favour immediate appendicectomy in every case of appendicitis.

Controversy over the conservative management of appendix mass has arisen mainly from the belief that children, and particularly infants, have a poor ability to localize intraperitoneal inflammatory processes. A child's ability to localize inflammation is well developed, however, even in infancy; one-half of the children who develop appendicitis during the first 2 years of life[5], and one-third in the first 3 years[1], have an appendix mass at the time of presentation.

In this study, the experience of conservative management of an appendix mass in the three Dublin children's hospitals during 19 years is reviewed.

Patients and methods

A total of 427 children presented to one of Dublin's three paediatric hospitals with an appendix mass during the interval from 1982 to 2000. Some 198 of these children have been reported in a previous study and were included in the present study[4]. There were 222 boys and 205 girls. Their ages ranged from 2 months to 18 years (mean 7·3 years). The duration of symptoms ranged from a few hours to

21 days; 266 (62·3 per cent) had symptoms for longer than 3 days. The diagnosis was made clinically in 136 children (31·9 per cent), by ultrasonography in 61 (14·3 per cent), by examination under anaesthesia in 229 (53·6 per cent) and by computed tomography in one child (0·2 per cent).

Conservative management consisted of close observation of the clinical course to identify any deterioration. Antibiotics were initially given parenterally, progressing to oral administration as the child's condition improved. Three hundred and forty (82·7 per cent) of 411 patients managed conservatively were given ampicillin, gentamicin and metronidazole, 23 (5·6 per cent) received given co-amoxiclav and metronidazole, 43 (10·5 per cent) had gentamicin and metronidazole, and five children (1·2 per cent) received various other antibiotic regimens. Children were allowed oral fluids and diet as tolerated. They were deemed to have responded to conservative management once free from abdominal pain, and once their pulse rate and temperature had been within normal limits for 48 h. Once the children were fit for discharge they were allowed home with planned elective appendicectomy 4–6 weeks later.

Results

Sixteen of the 427 children had an immediate appendicectomy following the diagnosis of appendix mass. In most of these cases a consultant surgeon performed the procedure. The median length of stay for these children was 6 (range 5–15) days. There were two postoperative complications: one wound infection and one pelvic abscess that required drainage.

Successful conservative management

Conservative management was adopted in the remaining 411 children; 346 (84·2 per cent) of these responded to initial non-operative treatment. These children stayed in hospital for a median of 6 (range 3–24) days on their initial hospital admission. Three hundred and thirty-one children had an elective appendicectomy as planned, 4–6 weeks after discharge. Three children returned to hospital for 1–2 days for observation of abdominal pain that settled spontaneously. These children all had a subsequent elective appendicectomy. Four children failed to return for surgery on the planned date, but subsequently presented to the hospital for emergency appendicectomy after 10, 10, 12 and 32 weeks. Eight children failed to return for elective appendicectomy and were lost to follow-up. The complication rate following elective appendicectomy was 2·3 per cent (eight patients – five wound infections, two intra-abdominal abscesses and one haematoma). Fifteen of the elective appendicectomies were performed laparoscopically; there were no postoperative complications in this group. The median hospital stay for uncomplicated elective appendicectomy was 3 (range 1–6) days. If the children who developed postoperative complications after elective appendicectomy are included, the mean hospital stay was 3·3 (range 1–30) days.

Failed conservative management

Sixty-five children (15·8 per cent) with an appendix mass failed to respond to initial non-operative management. Seventeen children deteriorated while under observation and required early appendicectomy. Eight of these had postoperative complications: four wound infections, two intra-abdominal abscesses and two small bowel obstructions. Twenty-seven children developed an appendix abscess during the initial admission and required incision and drainage with subsequent appendicectomy. The median length of stay in this group was 17 (range 10–44) days. There were two postoperative complications: one wound infection and one wound sinus that continued to discharge for 4 weeks.

Three children returned to hospital and required intravenous antibiotics and an admission of 4, 5 and 8 days for the treatment of an intra-abdominal abscess. They subsequently underwent elective appendicectomy.

Eighteen children came back to hospital before their planned elective appendicectomy with acute appendicitis and required appendicectomy. One of these children developed a small bowel obstruction 6 months after elective appendicectomy that failed to respond to conservative management. This child required a laparotomy to release a peritoneal adhesion. The median length of stay for all 65 patients who failed to respond to conservative management was 13·5 (range 5–44) days.

Elective appendicectomy

One hundred and sixty-eight (50·8 per cent) of the 331 elective appendicectomy histological specimens showed signs of acute or subacute inflammation; 42 specimens showed no evidence of pathology. Some 105 specimens were reported as showing chronic inflammation and in 14 children histological findings were not available. Two of the 331 elective appendicectomy specimens had histological evidence of carcinoid tumour.

Thirty-three appendix specimens (7·7 per cent) were found to have a faecolith. Four of these were diagnosed before operation on ultrasonography. The rest were identified at operation or on examination of the pathology specimen. Of the 33 children who had a faecolith, four were identified on examination of routine elective appendicectomy specimens and six children who required early appendicectomy were shown to have a faecolith. A faecolith was found in 11 of the children who required drainage of an appendix abscess and in 12 of those who had a recurrence of symptoms and required early appendicectomy.

Discussion

Appendicectomy in the presence of an appendix mass is a far more technically challenging procedure with an increased incidence of complications compared with routine appendicectomy. Increased blood loss and inadvertent damage to the bowel wall are among the recognized problems of morbidity. Appendicectomy is often performed by a trainee surgeon outside normal operating list hours. Performing an appendicectomy on an elective list ensures a full complement of hospital staff, should any difficulties be encountered. In the present review, 16 children had immediate appendicectomy in the presence of an appendix mass; most of these procedures were performed by a consultant during normal theatre working hours. Preoperative examination of a child's abdomen under anaesthesia should be an essential part of an appendicectomy. Failure to do so may lead to the inadvertent opening of an appendix mass. Considering these issues, the safest management of these children should be adopted; previous work by the authors, in a study of 198 children, advocated a conservative policy when an appendix mass was identified during examination under anaesthesia[4].

In this series 17 children required appendicectomy after the appendix mass did not respond to conservative management; eight of the 17 developed postoperative complications. The complication rate after elective appendicectomy was markedly lower, at 2·3 per cent. This difference should not immediately be accepted as evidence that elective appendicectomy is safer; it is likely that children who failed to respond to conservative treatment had more severe appendicitis. The only true way of comparing the two treatments for appendix mass is with a randomized controlled trial; as yet, no trials in children exist. The present results indicate that conservative treatment of an appendix mass followed by elective appendicectomy is safe and effective in children.

There are a number of outstanding issues. Conservative management of an appendix mass followed by elective appendicectomy entails a longer total hospital stay than immediate appendicectomy. In this review immediate appendicectomy entailed a median stay of 6 days, compared with a total hospital stay of 9 days for children with conservatively managed appendix masses, although the number of children who had immediate surgery ($n = 16$) was small.

Another issue is whether an appendix mass that has responded to conservative management requires a subsequent appendicectomy. Nitecki *et al.*[6] believe that elective appendicectomy is unnecessary, arguing that only 14 per cent of children have recurrent symptoms. This is a view shared by Ein and Shandling[7], who point out that of a group of ten children with an appendix mass only one returned with appendicitis following initial non-operative treatment. Not all agree. Price *et al.*[8] strongly advocate elective appendicectomy after seeing two patients return with acute appendicitis following initial conservative management of an appendix mass. Of 54 patients who were treated conservatively by Gahukamble and Gahukamble[9], 22 failed to return for elective appendicectomy. Seven of these presented at a later date with recurrent appendicitis. In this study 25 of 39 specimens removed at elective appendicectomy had evidence of a patent lumen on histological examination. It is claimed that this allows further inflammation and possibly recurrent appendicitis[10].

In the present review, acute or subacute inflammation was evident in 168 of 331 specimens removed at elective appendicectomy. Also, two cases of carcinoid tumour were discovered that would not have been found so promptly if appendicectomy had not been performed. The significance of lack of inflammation is less clear-cut. Ein and Shandling[7] believe it possible that inflammation can regress.

The presence of a faecolith was associated with increased morbidity in the present series. This agrees with the findings of Nitecki *et al.*[11] that complicated appendicitis is more likely to involve a faecolith; these authors recommend appendicectomy on finding a faecolith incidentally. In their review of pathology specimens, however, faecoliths were found in 42 per cent of appendix abscesses in adults, a significantly higher incidence than that in children in the present review. This low incidence and the presence of ongoing inflammation in resected appendix specimens implies that the decision to proceed to interval appendicectomy cannot be based purely on radiological evidence of a faecolith.

Examination under anaesthesia is performed by the authors on all children before appendicectomy. It could be argued that identification of an appendix mass represents unnecessary anaesthesia. An increasing number of appendix masses are identified by preoperative ultrasonography. The way in which the diagnosis was made did not influence the incidence of complications, either on the initial admission or for the subsequent interval appendicectomy, in this review. However, appendix masses discovered under anaesthesia had a shorter duration of symptoms (median 2 days) than those diagnosed clinically or by ultrasonography (median 4 days in both groups).

In the present series, of the 346 children who responded to initial conservative management, 12 failed to return for their appointed elective appendicectomy. Four of these children subsequently came back with recurrent appendicitis, a figure in line with Gahukamble and Gahukamble's experience[9]. This supports the current treatment protocol of initial non-operative management of appendix mass followed by elective appendicectomy.

Acknowledgements

The authors are grateful to Professor R. J. Fitzgerald and Mr F. M. J. Quinn for the inclusion of their patients in this study.

References

1 Puri P, Boyd E, Guiney EJ, O'Donnell B. Appendix mass in the very young child. *J Pediatr Surg* 1981; **16:** 55–7.
2 Puri P, O'Donnell B. Management of appendiceal mass in children. *Pediatr Surg Int* 1989; **4:** 306–8.
3 Geirup J, Karpe B. Aspects on appendiceal abscess in children with special reference to delayed appendicectomy. *Acta Chirurgica Scandinavica* 1975; **141:** 801–3.
4 Surana R, Puri P. Appendiceal mass in children. *Pediatr Surg Int* 1995; **10:** 79–81.
5 Puri P, O'Donnell B. Appendicitis in infancy. *J Pediatr Surg* 1978; **13:** 173–4.
6 Nitecki S, Assalia A, Schein M. Contemporary management of the appendiceal mass. *Br J Surg* 1993; **80:** 18–20.
7 Ein SH, Shandling B. Is interval appendicectomy necessary after rupture of an appendiceal mass? *J Pediatr Surg* 1996; **31:** 849–50.
8 Price MR, Haase GM, Sartorelli KH, Meagher DP. Recurrent appendicitis after initial conservative management of appendiceal abscess. *J Pediatr Surg* 1996; **31:** 291–4.
9 Gahukamble DB, Gahukamble LD. Surgical and pathological basis for interval appendicectomy after resolution of appendicular mass in children. *J Pediatr Surg* 2000; **35:** 424–7.
10 Mazziotti MV, Marley EF, Winthrop AL, Fitzgerald PG, Walton M, Langer JC. Histopathologic analysis of interval appendectomy specimens: support for the role of interval appendectomy. *J Pediatr Surg* 1997; **32:** 806–9.
11 Nitecki S, Karmeli R, Sarr MG. Appendiceal calculi and fecaliths as indications for appendectomy. *Surg Gynecol Obstet* 1990; **171:** 185–8.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk*

Expression of gastrin in developing gastric adenocarcinoma (*Br J Surg* 2001; 88: 564–8)

Sir

I agree with the authors that gastrin seems to be an important growth factor in gastric carcinogenesis. To determine if serum gastrin measurement could have an association with resectability and survival in patients with gastric carcinoma, my colleagues and I carried out a prospective study[1] and found that preoperative hypergastrinaemia is associated with unresectability and poor survival. Henwood *et al.* showed that increasing progastrin, gastrin/cholecystokinin B receptor, glycine-extended gastrin and amidated gastrin expression occurred along the pathway from atrophic gastritis to gastric carcinoma. The authors did not mention the correlation of gastrin expression with clinical outcome.

To connect their study with clinical practice, I believe the authors must answer the following questions. What was the number of *Helicobacter pylori* infected samples, or were they excluded? Did you correlate the expression of gastrin with serum gastrin levels? What was the treatment used for these patients? If you consider extent of resection, patient survival, metastasis and recurrence, did you find any difference between patients with high and low gastrin expression?

A. Soran
National Surgical Adjuvant Breast and Bowel Project Center
One Sterling Plaza
201 North Craig Street, Suite 350
Pittsburgh
PA 15231
USA

1 Soran A, Aslar AK, Col C. Are preoperative serum gastrin levels related to resectability and survival in gastric cancer? *Int J Clin Pract* 2000; **54:** 652–3.

Authors' reply

Sir

The relevance of hypergastrinaemia to clinical outcome is a separate issue from the detection of gastrin gene activation in developing neoplasms. Serum gastrin levels may be elevated through a number of distinct mechanisms not associated with activation of the gastrin gene such as *Helicobacter pylori* infection and following treatment with proton pump inhibitors. Such conditions result in over-secretion of amidated forms by the G cell whereas an activated gastrin gene in epithelial tumours leads to the predominance of non-amidated gastrin forms[1]. Other important studies have clarified this, and in patients with colorectal cancer non-amidated gastrin levels are indeed raised and subsequently reduced following tumour resection[2].

Our study was focused upon expression of the gastrin gene during the development of gastric adenocarcinoma. Our hypothesis was based on studies delineating the role of gastrin gene activation in the adenoma : carcinoma sequence in the colon, with the gene being a target of β-catenin mediated transcription[3]. Maximal activation of the gastrin gene in the samples with greater malignant potential suggests a correlation with poor clinical outcome. Oncogenes such as K-*ras* have been shown to maximize gastrin gene transcription[4], which would follow the premise that *de novo* activation of mitogenic and transcriptional activators such as gastrin and K-*ras* contributes to the malignant cascade.

In the context of our study, *H. pylori* infection has limited relevance, as there is no literature showing that *H. pylori* has any bearing on gastrin gene activation. As the majority of these samples were premalignant and obtained from patients undergoing endoscopic surveillance, the consideration of parameters such as metastasis and recurrence is irrelevant.

S. A. Watson
A. M. Smith
Cancer Studies Unit
Queen's Medical Centre
University Hospital
Nottingham NG7 2UH
UK

1 Ciccotosto GD, McLeish A, Hardy KJ, Shulkes A. Expression, processing, and secretion of gastrin in patients with colorectal carcinoma. *Gastroenterology* 1995; **109:** 1142–53.
2 Siddheshwar RK, Gray JC, Kelly SB. Plasma levels of progastrin but not amidated gastrin or glycine extended gastrin are elevated in patients with colorectal carcinoma. *Gut* 2001; **48:** 47–52.
3 Koh TJ, Bulitta CJ, Fleming JV, Dockray GJ, Varro A, Wang TC. Gastrin is a target of the beta-catenin/TCF-4 growth-signaling pathway in a model of intestinal polyposis. *J Clin Invest* 2000; **106:** 533–9.
4 Nakata H, Wang SL, Chung DC, Westwick JK, Tillotson LG. Oncogenic *ras* induces gastrin gene expression in colon cancer. *Gastroenterology* 1998; **115:** 1144–53.

Cost–utility analysis of open *versus* laparoscopic groin hernia repair: results from a multicentre randomized clinical trial (*Br J Surg* 2001; 88: 653–61)

Sir

To enter this trial each surgeon was required to have experience of ten laparoscopic herniorrhaphies. We consider this level of experience inadequate for appropriate evaluation of what is a technically challenging procedure. The resultant mean operating time of 58 min would be considered excessive in dedicated minimally invasive units, where mean procedural duration is 40 min or less[1,2]; this alone would almost result in a cost parity between laparoscopic and open techniques. The addition of capital costs for operating equipment (camera, etc.) of £29 961·18 to laparoscopic herniorrhaphy is inappropriate as this equipment would be available for the performance of laparoscopic cholecystectomy. If reusable equipment is utilized (we utilize reusable ports, needle holders, suture peritoneum (transabdominal preperitoneal procedure) and place mesh freely within space) there is a saving of £230·00 per patient. Contrary to the trial protocol, in most minimally invasive centres currently undertaking laparoscopic herniorrhaphy the majority of procedures are performed by experienced junior staff and most patients are treated as day-cases, resulting in considerable reduction in hospital expenditure[1]. The further financial saving related to diagnosis and concomitant treatment of covert contralateral hernias (incidence up to 50 per cent)[3] has not been factored into this analysis. Finally, there is no analysis of the reduction in societal costs related to earlier return to work with the laparoscopic procedure[4].

In a climate where recommendation of surgical procedures is being based primarily on cost[5], this paper does not do economic justice to laparoscopic herniorrhaphy as performed in dedicated centres where laparoscopic surgery is more cost-efficient.

C. J. O'Boyle
C. M. S. Royston
P. C. Sedman
Department of Upper Gastrointestinal and
Minimally Invasive Surgery
Hull Royal Infirmary
Anlaby Road
Hull HU3 2JZ
UK

1 Kapiris SA, Brough WA, Royston CMS, O'Boyle CJ, Sedman PC. Laparoscopic transabdominal preperitoneal (TAPP) hernia repair – a 7-year two-centre experience in 3017 patients. *Surg Endosc* 2001 (in press).
2 Quilici PJ, Greaney EM Jr, Quilici J, Anderson S. Laparoscopic inguinal hernia repair: optimal technical variations and results in 1700 cases. *Am Surg* 2000; **66:** 848–52.
3 Crawford DL, Hiatt JR, Phillips EH. Laparoscopy identifies unexpected groin hernias. *Am Surg* 1998; **64:** 976–8.
4 Heikkinen TJ, Haukipuro K, Hulkko A. A cost and outcome comparison between laparoscopic and Lichtenstein hernia operations in a day-case unit. A randomized prospective study. *Surg Endosc* 1998; **12:** 1199–203.
5 National Institute for Clinical Excellence. *Guidance on the Use of Laparoscopic Surgery for Inguinal Hernia.* Technology Appraisal Guidance – no. 18, January 2001.

Author's reply

Sir

The addition of capital costs for equipment used is entirely appropriate and an accepted economic method[1]. The capital cost per patient was based on annual patient utilization, including non-hernia use. The extra 15 min operating time for laparoscopic repair reported is representative: weighted mean difference in 37 relevant randomized clinical trials is 14·8 (95 per cent c.i. 14·0–15·6) min[2].

Our report included a re-usable only scenario, reducing mean operative costs of laparoscopic repair by £180·00 – close to the £230·00 suggested by your correspondent.

We recognize that open and laparoscopic repair can be carried out as day-case procedures. The Medical Research Council (MRC) analyses, however, were based on equivalent hospital stay, as would apply in dedicated centres. The advantage of this trial was its large, simple, pragmatic nature capturing standard practice variation in National Health Service (NHS) general surgical wards.

The potential benefit of identifying occult contralateral hernias remains conjecture. This applies to the transabdominal approach rather than the totally extraperitoneal approach mainly used in our trial.

Contrary to the above assertion, our study reported estimates of early return to work. Given unresolved theoretical concerns with including productivity gains[3], the trial provided only descriptive productivity information without attaching potentially discriminatory values. Since societal values are generally excluded from cost–effectiveness ratios, the MRC information was not only supplementary but unbiased.

The MRC costs reflected standard NHS surgical practice variation, not an evaluation of a dedicated minimally invasive centre. Economies of scale and patient selection criteria (young, fit working adults) undoubtedly make it likely that laparoscopic surgery will be more cost-effective in such centres.

Finally, surgical procedures are not being recommended primarily on cost but on cost-effectiveness – a different concept altogether.

Medical Research Council Laparoscopic
Groin Hernia Trial Group
Health Economics Research Unit and Health Services Unit
University of Aberdeen
University Medical Buildings
Foresterhill
Aberdeen AB25 2ZD
UK

1 Webb K, Scott NW, Go PMNYH, Ross S, Grant AM, on behalf of the EU Hernia Trialists Collaboration. Laparoscopic techniques *versus* open techniques for inguinal hernia repair. In: *The Cochrane Library. Issue 4.* Oxford: Update Software, 2000.
2 Drummond MF, Stoddart GL, Torrance W. *Methods for the*

Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press, 1987.
3 Pritchard C, Sculpher M. *Productivity Costs: Principles and Practice in Economic Evaluation*. London: Office of Health Economics, 2000.

Randomized clinical trial of the effect of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer (*Br J Surg* 2001; 88: 801–7)

Sir

The authors conclude that the systemic immune response is activated equally after both procedures. Previous publications from our clinic and from others suggest otherwise. In 1994 Kloosterman *et al.*[1] were one of the first groups to demonstrate significant differences between laparoscopic and conventional cholecystectomy. They studied monocyte human leucocyte antigen (HLA)-DR expression as a parameter for trauma induced immune suppression. Sietses *et al.*[2] confirmed these results in a randomized clinical study comparing both techniques for Nissen fundoplication. In both studies a significant difference was noticed in the postoperative expression of the HLA-DR antigen on monocytes, favouring the laparoscopic approach. Wakefield *et al.*[3] demonstrated that reduced HLA-DR expression on monocytes and slow restoration to preoperative values after surgical intervention is associated with an increased incidence of infection. These differences, however, were only found 1 day after surgery.

The measurements in this trial were performed 3 days after surgery, and therefore probably too late to demonstrate any differences between the two techniques.

F. P. K. Wu
M. A. Cuesta
C. Sietses*
Department of Surgery
Medical Centre Vrije Universiteit
De Boelelaan 1117
1081 HV Amsterdam
**Department of Surgery*
Medical Centre Alkmaar
Wilhelminalaan 12
1815 JD Alkmaar
The Netherlands

1 Kloosterman T, von Blomberg BM, Borgstein P, Cuesta MA, Scheper RJ, Meijer S. Unimpaired immune function after laparoscopic cholecystectomy. *Surgery* 1994, **115**: 424–8.
2 Sietses C, Wiezer MJ, Eijsbouts QAJ, Beelen RH, van Leeuwen PA, von Blomberg BM *et al.* A prospective randomized study of the systemic immune response after laparoscopic and conventional Nissen fundoplication. *Surgery* 1999; **126**: 5–9.
3 Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993; **80**: 205–9.

Totally extraperitoneal endoscopic repair of recurrent inguinal hernia (*Br J Surg* 2001; 88: 884–6)

Sir

This retrospective review of totally extraperitoneal (TEP) repair of 108 recurrent hernias showed a 2 per cent recurrence rate at a median follow-up of 16 months. The authors do not expect an increase in recurrence rate and conclude that, despite the relatively short follow-up, TEP repair is safe and effective for the repair of recurrent inguinal hernia.

This conclusion is consistent with most recent TEP repair reports[1–4], claiming a recurrence rate of 0·3–2 per cent at follow-up from 3 months[2] to more than 6 years[4]. The common methodological problem of these and many other studies is the adequacy of the follow-up period. Nearly 50 per cent of recurrences first appear 5 years after surgery and many patients are lost to follow-up, including those who seek care at other centres. Statistical significance is best determined with a 10-year follow-up[5].

This paper does not discuss the long-term complication rate – a common problem with mesh hernia repair[6]. The relevance of the cumulative risk for long-term complications, such as mesh migration and fistula formation, the extent of patient complaints, or the potential risk of a persistent foreign-body reaction are not explored. A much larger study with a long-term follow-up is needed to demonstrate whether TEP repair is genuinely superior to other methods. The authors are correct in noting that avoidance of common complications of intra-abdominal surgery is one of the primary advantages of preperitoneal mesh hernioplasty. None the less, the good results of these and other investigators[1–4] should be regarded as short-term outcomes only. Claimed advantages of TEP repair should be weighed against the 'gold standard' of open mesh repair[7,8].

J. E. Losanoff
J. W. Jones
B. W. Richman
Department of Surgery
University of Missouri – Columbia
One Hospital Drive
Columbia
MO 65212
USA

1 Aeberhard P, Klaiber C, Meyenberg A, Osterwalder A, Tschudi J. Prospective audit of laparoscopic totally extraperitoneal inguinal hernia repair: a multicenter study of

the Swiss Association for Laparoscopic and Thoracoscopic Surgery (SALTC). *Surg Endosc* 1999; **13:** 1115–20.
2 Memon MA, Feliu X, Sallent EF, Camps J, Fitzgibbons RJ Jr. Laparoscopic repair of recurrent hernias. *Surg Endosc* 1999; **13:** 807–10.
3 Lepere M, Benchetrit S, Debaert M, Detruit B, Dufilho A, Gaujoux D *et al.* A multicentric comparison of transabdominal *versus* totally extraperitoneal laparoscopic hernia repair using PARIETEX meshes. *JSLS* 2000; **4:** 147–53.
4 Ramshaw B, Shuler FW, Jones HB, Duncan TD, White J, Wilson R *et al.* Laparoscopic inguinal hernia repair: lessons learned after 1224 consecutive cases. *Surg Endosc* 2001; **15:** 50–4.
5 Lichtenstein I. *Hernia Repair Without Disability*, 2nd ed. St Louis, Missouri: Ishiyaku EuroAmerica, 1987: 163–6.
6 Schumpelick V, Klinge U, Welty G, Klosterhalfen B. Meshes within the abdominal wall. *Chirurg* 1999; **70:** 876–87.
7 EU Hernia Trialists Collaboration. Laparoscopic compared with open methods of groin hernia repair: systematic review of randomized controlled trials. *Br J Surg* 2000; **87:** 860–7.
8 Smith JR, Demers ML, Pollack R, Gregory S. Prospective comparison between laparoscopic preperitoneal herniorrhaphy and open mesh herniorrhapy. *Am Surg* 2001; **67:** 115–17.

Authors' reply

Sir

The value of well controlled follow-up studies of endoscopic repair of inguinal hernias using prosthetic material is not questioned and there is a need for more long-term data on this technique. It has been shown, however, that most recurrences after totally extraperitoneal repair occur early[1]. In patients in whom a mesh graft was used, but introduced by other techniques, the long-term presence of mesh did not result in significant numbers of complications[2,3]. We believe that late complications related to mesh graft implantation will have a low incidence.

J. A. van der Hem
J. F. Hamming
J. D. Meeuwis
H. J. M. Oostvogel
Department of Surgery
St Elisabeth Hospital
Tilburg
The Netherlands

1 Felix EL, Michas CA, Gonzalez MH Jr. Laparoscopic hernioplasty. TAPP *vs* TEP. *Surg Endosc* 1995; **9:** 984–9.
2 Rutkow IM, Robbins AW. The mesh plug technique for recurrent groin herniorrhaphy: a nine-year experience of 407 repairs. *Surgery* 1998; **124:** 844–7.
3 Wantz GE. Giant prosthetic reinforcement of the visceral sac. The Stoppa groin hernia repair. *Surg Clin North Am* 1998; **78:** 1075–87.

Management of aortic aneurysm in the presence of a horseshoe kidney (*Br J Surg* 2001; 88: 500–9)

Letter 1

Sir

The review of management of aortic aneurysm in the presence of a horseshoe kidney was of interest to us as we had recently managed a patient with a ruptured abdominal aortic aneurysm (AAA) with this rare complication. In the review, the authors noted that the level of aortic cross-clamping was infrequently described and this limited the conclusions which could be drawn on the level of clamping on renal function.

Our patient was an 81-year-old gentleman who presented to a neighbouring hospital for investigation of urinary symptoms. Computed tomography revealed a 9-cm diameter AAA associated with a horseshoe kidney. While in hospital the aneurysm ruptured. The aneurysm was approached through a midline incision and the aorta clamped suprarenally. This caused 'deflation' of the horseshoe kidney, making both the kidney and aneurysm easier to handle. The upper anastomosis of the bifurcated aortic graft was fashioned around the orifices of both renal arteries, allowing a further clamp to be applied to the graft below the upper anastomosis and the suprarenal clamp to be released. Haemostasis was achieved without the need for further sutures and kidney reperfusion was demonstrated by its 're-inflation' and return of normal colour. Renal ischaemic time was only 17 min. Both limbs of the bifurcated graft were tunnelled through the sac underneath the intact parenchymatous renal isthmus and anastomosed to the common iliac arteries, below the level of the horseshoe kidney. The patient required 9 units of blood intraoperatively and urine output was minimal during surgery.

As described in the review, the main postoperative complication was acute renal failure, which was possibly exacerbated initially by his pre-existing bladder outflow obstruction. He spent 7 days in the intensive care unit and required several days of haemofiltration. We were interested to note that development of renal insufficiency after rupture is a poor prognostic indicator with about a 90 per cent mortality rate. We are pleased to report that our patient is alive and well in the community 4 months after his surgery.

T. Tang
S. Hanna
M. Gaunt
Department of Vascular Surgery
Box 201
Addenbrooke's Hospital
Cambridge CB2 2QQ
UK

Letter 2

Sir

We challenge the conclusion of the authors that division of the isthmus of the kidney should be avoided in all patients. We recently managed two patients in whom the horseshoe kidney was discovered at laparotomy and in both the diagnosis was missed by ultrasonography. Division of the isthmus of the horseshoe kidney allowed adequate exposure of the aneurysm and repair to be carried out safely.

A review of the literature suggests that in this situation, with a transperitoneal approach, division of the isthmus may be necessary in approximately 34 per cent of patients[1]. A factor counting against division of the isthmus is the increased risk of urinary fistula, because the isthmus may contain elements of the collecting system[2,3] and graft sepsis is a potential risk[4]. It has been suggested that there is an increased risk of haemorrhage from the divided renal parenchyma and renal necrosis but none of these complications have been reported in the literature. The paper quoted to support this view does not report any of the mentioned complications[5]. We conclude that division of the isthmus can safely enhance access for transperitoneal repair of aneurysm.

C. McIlhenny
R. N. Scott
Department of Surgery
Monklands Hospital
Airdrie ML6 0JS
UK

1 Connelly TL, McKinnon W, Smith RB III, Perdue GD. Abdominal aortic surgery and horseshoe kidney. *Arch Surg* 1980; **115**: 1459–63.
2 Pelmutter AD, Retick AB, Bauer SB. Anomalies of the upper urinary tract. In: Walsh PC, ed. *Campbell's Urology*, 6th ed. Philadelphia, Pennsylvania: WB Saunders, 1992: 1357–442.
3 Bomalaski MD, Gardner AL, Madison DL. Aortic surgery complicated by horseshoe kidney. *Indiana Med* 1988; **81**: 688–93.
4 Shortell CK, Welch EL, Ouriel K, Green RM, DeWeese JA. Operative management of co-existent aortic disease and horseshoe kidney. *Ann Vasc Surg* 1995; **9**: 123–8.
5 Glenn JF. Analysis of 51 patients with horseshoe kidney. *New Engl J Med* 1959; **261**: 684–7.

Authors' reply

Sir

The contribution of Tang *et al.* underlines the conclusions of our publication.

Division of the renal isthmus after a transperitoneal approach does not always lead to complications such as haemorrhage or urinary fistula. However, in contrast to the assertion of McIlhenny *et al.* these complications are well documented, not only after division as treatment of ureteropelvic junction obstruction[1,2] but also after division of a horseshoe kidney prior to transplantation[3–5]. We realize that division of the isthmus may be necessary to allow adequate exposure when the aneurysm is approached transperitoneally but this should be avoided when possible, for example, by using a retroperitoneal approach.

O. B. Stroosma
G. W. H. Schurink
Department of Surgery
University Hospital Maastricht
PO Box 5800
6202 AZ Maastricht
The Netherlands

1 Dajani AM. Horseshoe kidney: a review of twenty-nine cases. *Br J Urol* 1966; **37**: 388–402.
2 Culp OS, Winterringer JR. Surgical treatment of a horseshoe kidney: comparison of results after various types of operations. *J Urol* 1955; **73**: 747–56.
3 Stroosma OB, Scheltinga MRM, Stubenitsky BM, Kootstra G. Horseshoe kidney transplantation: an overview. *Clin Transplant* 2000; **14**: 515–19.
4 Stroosma OB, Smits JMA, Schurink GWH, de Boer J, Persijn GG, Kootstra G. Horseshoe kidney transplantation within the Eurotransplant region: a case control study. *Transplantation* (in press).
5 Stroosma OB, Schurink GWH, Smits JMA, Kootstra G. Transplanting horseshoe kidneys: a world-wide survey. *J Urol* (in press).

Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy (*Br J Surg* 2001; 88: 669–74)

Sir

The authors report a median length of stay of 1 (range 0–3) day after stapled haemorrhoidectomy which compared favourably with a median stay of 2 (range 0–12) days in the Milligan–Morgan group and concluded the former to be superior to conventional surgery. In support of their argument they have misrepresented our study[1]: 'The median hospital stay of the Milligan–Morgan group is comparable to the 2·5 days reported by Bleday *et al.* and Carapeti *et al.*'. In fact all patients in our study were treated as day cases and discharged within 6 h of surgery as clearly stated even in the title of the article. Similarly, the authors misrepresent our second study[2], quoting no advantage in the use of antibiotics. In this study a clear advantage was seen with postoperative metronidazole compared to placebo in reducing pain after diathermy haemorrhoidectomy. Finally they state that failure of the various measures employed previously to reduce pain is because 'the main unsolved problem is that the sensitive anal mucosa is severely traumatized during haemorrhoidectomy'. However, in their study they have provided no nociceptive data or electrophysiological measurements to support such a claim which must merely remain their own hypothesis. On the other hand, clear data now exist showing that open and closed haemorrhoidectomy using diathermy (or other conventional techniques) can be carried out to high patient satisfaction as a day-case procedure without the need for either a costly stapler device or a hospital stay of up to 3 days.

E. A. Carapeti
Department of Surgery
St Thomas' Hospital
London SE1 7EH
UK

1 Carapeti EA, Kamm MA, McDonald PJ, Chadwick SJD, Phillips RKS. Randomized trial of open *versus* closed day-case haemorrhoidectomy. *Br J Surg* 1999; **86:** 612–13.
2 Carapeti EA, Kamm MA, McDonald PJ, Phillips RKS. Double-blind randomised controlled trial of effect of metronidazole on pain after day case haemorrhoidectomy. *Lancet* 1998; **351:** 169–72.

Author's reply

Sir

Mr Carapeti's letter shows how varied patients' and surgeons' perception of this common disease can be. For his first point, a wrong quotation was used (rather than a misinterpretation of the study) and for this we apologize. The conclusion of our randomized study, in which the Milligan–Morgan group had a longer hospital stay than the stapler group, remains the same. We believe that the early hospital discharge (6 h) claimed by Carapeti *et al.* cannot be applied to patients with third- and fourth-degree haemorrhoids. It is not specified in this paper what degree of haemorrhoids were treated.

With regards to the role of metronidazole in controlling postoperative pain they found reduced pain only after 5 days, when postoperative pain is also normally lessened. Most patients (95 per cent in our personal experience) treated with a stapler do not need analgesics after 2–3 days and the first defaecation is not painful.

Regarding the final point, two methods were employed for evaluating nociceptive data, a visual analogue scale and a composite pain score, both of which indicated superiority of the stapler technique. The cost of the stapler device is clearly a problem. The advantages of reduced postoperative pain and earlier hospital discharge and return to work provide strong counterbalance arguments. The economic problem will probably not stop the increasing popularity of this new surgical technique.

D. F. Altomare
Department of Emergency Medicine and Organ Transplantation
General Surgery and Liver Transplantation Unit
University of Bari
Policlinico
Piazza G Cesare
11–70124 Bari
Italy

Comprehensive Urology

R. M. Weiss, N. J. R. George and P. H. O'Reilly (eds)
285 × 218 mm. Pp. 724 Illustrated. 2001 London Mosby. £149·00.

On reading the preface I learnt that 'Urology today is a vibrant speciality at once embracing the expanding horizons of molecular biology, the complexities of pathophysiology and the solid bed rock of clinical observation and measurement'. With this first sentence alone I could see that the book was written for the American market although two of the three editors are in fact British. The editors then go on to state that the intention of the book is to provide comprehensive coverage of urology for trainees taking 'boards' and the older physician facing re-accreditation. I suspect on reading the book that it will appeal more to trainees than to consultants facing re-accreditation by virtue of the style that most of the authors have adopted. The authors who have been chosen by the editors are 'friends and colleagues worldwide who have helped conceive and project this unique approach to urological publishing'. Although several of the names will be unknown to the average reader, world authorities are included among the contributors and the overall standard from both groups is good.

Some chapters are particularly good, notably the one on superficial bladder cancer from Michael Wallace. The volume is lavishly illustrated and the quality of the illustrations in the anatomy chapter by John Gosling and John Dickson (which is up to their usual standard) is particularly good. Some of the magnetic resonance images elsewhere in the book have been reproduced less satisfactorily and an otherwise excellent chapter on trauma by Jack MacAninch and Michael Safir is marred by two radiographs that have been reproduced the wrong way round. I obviously wanted to know why I had not been asked to write for the book myself but could find no criticism whatsoever of the chapters on subjects I am particularly interested in, and I certainly learnt a great deal from those on subjects that I know less about (the vast majority). Having actually read the book (which is perhaps unusual for a reviewer) I feel reasonably confident about facing re-accreditation and I have already recommended the volume to my trainees. My final comments are that the pathology review right at the end of the book seems a little pointless (but this is a minor criticism), and that the chapter on the history of urology by Wyndham Lloyd Davis at the very beginning of the book is absolutely outstanding and quite the best short review of the subject I have ever read.

A. R. Mundy
Institute of Urology and Nephrology
Royal Free and University College Medical School
University College London
48 Riding House Street
London W1W 7EY
UK

ABC of Liver, Pancreas and Gall Bladder

I. J. Beckingham (ed.)
295 × 210 mm Pp. 54. Illustrated 2001. London BMJ Books. £16·95

Most of the books dealing with these subjects are heavy and cover all aspects extensively, mostly with the intention to be complete. I assume that this has not been the intention of the authors of this volume of the ABC series. However, in this book of only 54 pages almost all diseases of liver, pancreas and gallbladder are put together in such a way that it asks for appreciation. It is very complete with respect to clinical pictures and almost all forms of treatment are succinctly described. The text is illustrated with colour photographs, well selected radiological pictures and clear multicolour drawings. Schematic tables, called 'boxes', and flowcharts are very informative. Warnings and rules of thumb shaded with a blue background complete the text. All chapters end with summary points and a recommendation for further reading. This modern layout makes the book very pleasant to read or to look up a desired topic. The volume should not be considered as a textbook, but in just a few minutes it gives the reader a complete and clear picture of today's practice. It is particularly suitable for students, residents and anyone else who is interested in the field. Because of its completeness it is more than just an ABC.

T. Wobbes
Department of Surgery
University Medical Centre Nijmegen
PO Box 9101
6500 HB Nijmegen
The Netherlands

Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial that has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Tan JJ, Seow-Choen F. Prospective, randomized trial comparing diathermy and Harmonic Scalpel hemorrhoidectomy. *Dis Colon Rectum* 2001; **44:** 677–9.

There was no difference in the duration of surgery, analgesic requirements or postoperative pain scores in this study of 50 patients.

Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F *et al.* Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285:** 2331–8.

Some 129 of an original cohort of 239 patients were available for follow-up at a mean of 9–10 years. Some 92 per cent of medical and 62 per cent of surgical patients still needed antireflux drugs ($P < 0{\cdot}001$). Quality of life scores, the incidence of late complications and the rate of oesophageal malignancy were similar.

Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Coleridge Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. *Lancet* 2001; **357:** 1485–9.

A total of 231 patients with journeys over 8 h were randomized to class I graduated compression stockings or control groups. Duplex imaging revealed that 12 patients (all in the control group – 10 per cent) had symptomless deep vein thrombosis.

Look M, Chew SP, Tan YC, Liew SE, Cheong DM, Tan JC *et al.* Post-operative pain in needlescopic *versus* conventional laparoscopic cholecystectomy: a prospective randomised trial. *J R Coll Surg Edinb* 2001; **46:** 138–42.

There was no advantage of needlescopic over laparoscopic cholecystectomy in terms of postoperative pain ($P = 0{\cdot}49$), analgesia requirement ($P = 0{\cdot}93$), discharge or recovery rate in this study of 64 operations.

Hayes PD, Allroggen H, Steel S, Thompson MM, London NJ, Bell PR *et al.* Randomized trial of vein *versus* Dacron patching during carotid endarterectomy: influence of patch type on postoperative embolization. *J Vasc Surg* 2001; **33:** 994–1000.

Some 276 operations were included. The 30-day death or any stroke rate was similar: Dacron 2·2 per cent, vein 3·6 per cent (P not significant). The rate of sustained postoperative embolization requiring treatment was also similar: 5·3 *versus* 3·7 per cent respectively.

Delgado S, Lacy AM, Filella X, Castells A, Garcia-Valdecasas JC, Pique J *et al.* Acute phase response in laparoscopic and open colectomy in colon cancer: randomized study. *Dis Colon Rectum* 2001; **44:** 638–46.

In this study including 97 patients, levels of interleukin 6 and C-reactive protein were higher in the first 72 h after conventional open operation. There were no significant differences in cortisol or prolactin levels.

Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG *et al.* Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomized patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg* 2001; **22:** 107–13.

A total of 264 patients were randomized into one of three groups. Only patients who had surgery showed improvements in walking capacity, leg blood pressure and blood flow.

Lund JN, Scholefield JH, Grainge MJ, Smith SJ, Mangham C, Armitage NC *et al.* Risks, costs, and compliance limit colorectal adenoma surveillance: lessons from a randomised trial. *Gut* 2001; **49:** 91–6.

Some 776 patients were randomized into two groups, one at high and one at low risk of adenoma recurrence; various schedules of flexible sigmoidoscopy or colonoscopy were tested. Adenoma recurrence rates were low; surveillance could be targeted at high-risk groups with examination every 5 years.

Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H *et al.* Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy *versus* surgery alone. *Cancer* 2001; **91:** 2165–74.

The trial included 96 patients. Of the 48 patients who had preoperative chemotherapy, only those with complete histological remission had a significantly improved 5-year survival rate (60 per cent, $P < 0{\cdot}001$).

Barone JE, Tucker JB, Rassias D, Corvo PR. Routine perioperative pulmonary artery catheterization has no effect on rate of complications in vascular surgery: a meta-analysis. *Am Surg* 2001; **67:** 674–9.

Only four randomized studies were suitable for analysis; there was no evidence that pulmonary artery catheterization improved outcome in moderate-risk vascular patients.

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Instructions to authors

BJS publishes original articles, reviews and leading articles all of which are submitted to peer review.

An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject. It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap. Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Send four copies of original articles and other editorial matter to: The Editor, *BJS*, Blackwell Science Ltd, 25 John Street, London WC1N 2BS, UK. Telephone: 0207 404 1831; facsimile: 0207 404 1927. A version on disk must accompany all submitted material. For instructions on how to do this, see below. Books for review should be sent to the same address.

A covering letter must accompany all submissions, must be signed by all authors and must state whether an abstract of the work has been published - please provide an appropriate reference. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The Journal takes very seriously its obligation to assess and declare any actual or potential conflicts of interest. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support. The first named author is responsible for ensuring that all authors have seen, approved and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994, 308: 39–42) and the COPE guidelines on good publication practice (www.publicationethics.org.uk). If a paper has more than six authors you must justify the inclusion of all names. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995, 345: 668). The Editors are of the view that those with a peripheral association with the work should simply be acknowledged (*BJS* 2000; 87: 1284–6).

Disks

IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors. Proofs will be sent via e-mail as an Acrobat portable document format (PDF) file.

Rejected manuscripts and illustrations will not normally be returned.

Ethics

Material relating to human investigation and animal experiments must comply with and be approved by local ethics committees. It must conform to standards currently applied in the country of origin. The Journal reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication of any details or photographs that might identify an individual. Submit evidence of such consent with the manuscript.

Preparation of manuscripts

BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; 336: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

Reviews and meta-analyses of randomized trials

The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; 354: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent

electronically via the *BJS* website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (www.consort-statement.org).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the P value. Actual P values should be reported to three decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:[1] or [1–3]. References cited only in tables or figures should be numbered in sequence.

British Journal of Surgery

The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Society of Academic and Research Surgeons, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

Editorial Team

Editors
J. A. Murie, *Edinburgh, UK*
J. R. Farndon, *Bristol, UK*

Associate Editors
P. J. Guillou, *Leeds, UK*
P. R. O'Connell, *Dublin, Ireland*

Website Editor
J. J. Earnshaw, *Gloucester, UK*

Statistical Consultant
G. D. Murray, *Edinburgh, UK*

Council

Chairman
R. C. G. Russell, *London, UK*

Vice-Chairman
T. Bates, *Ashford, UK*

Treasurer
N. J. McC. Mortensen, *Oxford, UK*

Company Secretary
J. R. C. Sainsbury, *London, UK*

D. Alderson, *Bristol, UK*
J. Bancewicz, *Salford, UK*
M. Büchler, *Berne, Switzerland*
V. W. Fazio, *Cleveland, Ohio, USA*
K. C. H. Fearon, *Edinburgh, UK*
I. G. Finlay, *Glasgow, UK*
(Royal College of Surgeons)
P. Lamont, *Bristol, UK*
(Society of Academic and Research Surgeons)
M. Lee, *Birmingham, UK*
(Association of Surgeons)
J. P. Neoptolemos, *Liverpool, UK*
H. Obertop, *Amsterdam, The Netherlands*
M. Rothmund, *Marburg, Germany*
C. J. H. van de Velde, *Leiden, The Netherlands*

University College of Medicine C. U. Calcutta
LIBRARY

Editorial Board

W. H. Allum, *UK*
C. Bassi, *Italy*
J. Beynon, *UK*
N. J. Bundred, *UK*
W. B. Campbell, *UK*
F. Castro-Sousa, *Portugal*
S. C. S. Chung, *Hong Kong*
J. D. Corson, *USA*
D. Demetriades, *USA*
D. M. Dent, *South Africa*
C. Dervenis, *Greece*
T. Diamond, *UK*
L. Fernández-Cruz, *Spain*
A. Fingerhut, *France*
O. J. Garden, *UK*
D. Gotley, *Australia*
D. J. Gouma, *The Netherlands*
P. A. Grace, *Ireland*
U. Haglund, *Sweden*
M. Kitajima, *Japan*
Z. H. Krukowski, *UK*
G. J. Maddern, *Australia*
N. Nagasue, *Japan*
A. R. Naylor, *UK*
S. Nicholson, *UK*
B. Nordlinger, *France*
L. Påhlman, *Sweden*
A. L. G. Peel, *UK*
F. Penninckx, *Belgium*
L. F. Rikkers, *USA*
B. J. Rowlands, *UK*
S. Rudzki, *Poland*
F. Seow-Choen, *Singapore*
A. Sitges-Serra, *Spain*
O. Soreide, *Norway*
R. A. J. Spence, *UK*
M. D. Stringer, *UK*
K. Sugimachi, *Japan*
J. M. Thomas, *UK*
S. Vittal, *India*
T. N. Walsh, *Ireland*
A. L. Warshaw, *USA*
S. D. Wexner, *USA*
M. H. Wheeler, *UK*

While every effort is made by the Editorial Team, members of Council and the publishers to avoid inaccurate or misleading information appearing in *BJS*, data within the individual articles and advertisements are the responsibility of the authors or advertisers concerned. The BJS Society, the publishers, and members of the Editorial Team and Council accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

The *BJS* ISSN 0007-1323

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *BJS*, Blackwell Science Ltd,
25 John Street, London WC1N 2BS, UK (Tel: +44 0207 404 1831).

Manager	Elizabeth Whelan
Production Editor	Emma Missen (emma.missen@blacksci.co.uk)
Editorial Assistant	Mary Savigar

Aims and scope

BJS is the premier general surgical journal in Europe and one of the top surgical periodicals in the world. Its international readership is reflected in the prestigious international Editorial Board, supported by a panel of over 1200 reviewers worldwide.

BJS features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented.

The inclusion of Leading Articles, Reviews and Original Articles means that *BJS* offers an appropriate format for any length or type of submission; in addition, there are abstracts from key meetings, correspondence and book reviews. *BJS* will be of interest not only to general surgeons, but also to specialty surgeons and those working in related fields.

Subscriptions

BJS is published monthly (one volume per annum) in 2001. Print subscription prices for 2001 are:

	EUROPE	REST OF WORLD	NORTH AMERICA
Institutional	£146.00	£169.00	$261.00
Individual	£87.00	£101.00	$156.00
All Trainee Surgeons UK and ASIT	£43.50	£50.50	$78.50
Surgeons in Training Worldwide	£43.50	£50.50	$78.50

For online access in addition to print, please add 10 per cent to the print subscription price. For an online subscription without a print subscription, please pay 90 per cent of the print subscription price.

All members of the Association of Surgeons of Great Britain and Ireland, Surgical Research Society and Association of Surgeons of the Netherlands receive the paper journal as a benefit of membership of the society. In addition, all members have full access to the online version of the journal.

Subscribers in Canada must add 7% to the subscription price to allow for GST. Subscribers in Europe must quote their VAT registration number or state that they are not registered. Subscribers in the following countries who are not VAT-registered must add VAT at the appropriate rate:

- Belgium (6% TVA/BTW)
- France (2.1% TVA)
- Germany (7% MWST)
- Spain (4% IVA)
- The Netherlands (6% BTW)

Orders for current subscriptions and back issues should be sent to Blackwell Science Ltd, Journal Subscriptions, PO Box 88, Oxford OX2 0NE, UK. Tel: +44 1865 206180; Fax: +44 1865 206219; e-mail: jnl.orders@blacksci.co.uk

Despatch

BJS is despatched within the UK by second class post, within Europe by air mail, and to other continents by various forms of air-speeded delivery, to the USA by air freight for forwarding by second class post*, to India by air freight for guaranteed local delivery, and to all other countries by accelerated surface post. Add to the cost of a regular subscription £24.00/$36.00 for air mail delivery outside Europe.

Business correspondence

All other business correspondence, including orders for offprints (offprints@blacksci.co.uk) and advertising space (advert@blacksci.co.uk) should be addressed to:
BJS, Blackwell Science Ltd, Osney Mead,
Oxford OX2 0EL, UK. (Tel. +44 1865 206206;
Fax: +44 1865 721205).

Copyright and photocopying

© 2001 Blackwell Science, acting as agents for the BJS Society. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Science for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $15 per copy is paid directly to CCC, 222 Rosewood Drive, Suite 910, Danvers, MA 01973, USA. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to the publisher.

Paper

The Publisher's policy is to use acid-free permanent paper, to the draft standard ISO/DIS/9706, made from sustainable forests using chlorine-free pulp. The paper used in this journal has an ECO-CHECK 4-star rating.

BJS has a worldwide website at: http://www.bjs.co.uk

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or be transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of the publisher.

Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: *BJS*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

UNIVERSITY OF DUNDEE

SURGICAL SKILLS UNIT

The Surgical Skills Unit provides high quality skills training aimed at improving surgical competence and execution related to particular specialties. The training covers predominantly, but not exclusively, endoscopic skills at three levels: basic, advanced and procedure related.

A variety of courses are regularly available:

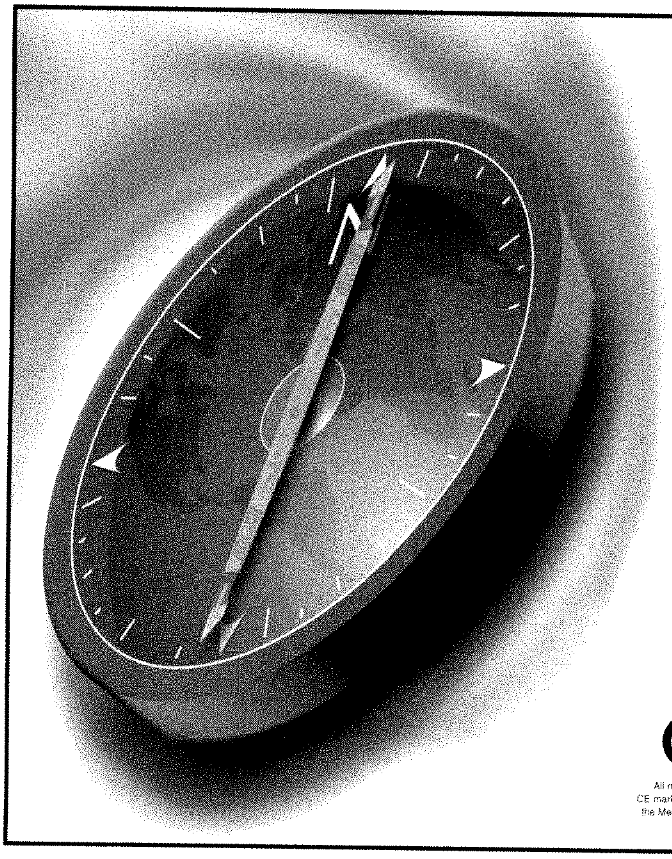
- **Essentials of Laparoscopic Surgery**
- **Advanced Endoscopic Surgery Skills**
- **Gynaecology**
- **Otolaryngology**
- **Anaesthetics**
- **Paediatrics**

Other specialist courses are held according to demand. Please contact us with your requirements.

Details of the Unit and all of our courses are available at:

www.dundee.ac.uk/surgicalskills

Contact: Mrs A Duncan
Surgical Skills Unit
Level 5, Ninewells Hospital and Medical School,
Dundee, DD1 9SY
Tel. 01382 645857 Fax 01382 646042



POINTING THE WAY TO PRECISION WORLDWIDE

All over the world, surgeons and medical practitioners appreciate the consistent quality and precision of Swann-Morton surgical blades and scalpels. With a network of agents and distributors covering the globe, Swann-Morton top-quality products can be accessed at any point of the compass.

As well as its comprehensive standard surgical ranges, the company also produces a 'Major' Orthopaedic range, a 'Fine' range, 'Minor' disposable scalpels, and specialised blades for myringotomy, cervical biopsy and skin graft. Where appropriate, products are sterilised using the in-house facilities of Swann-Morton (Services) Ltd.

Wherever you are in the world, make Swann-Morton your point of reference for your surgical blade requirements.

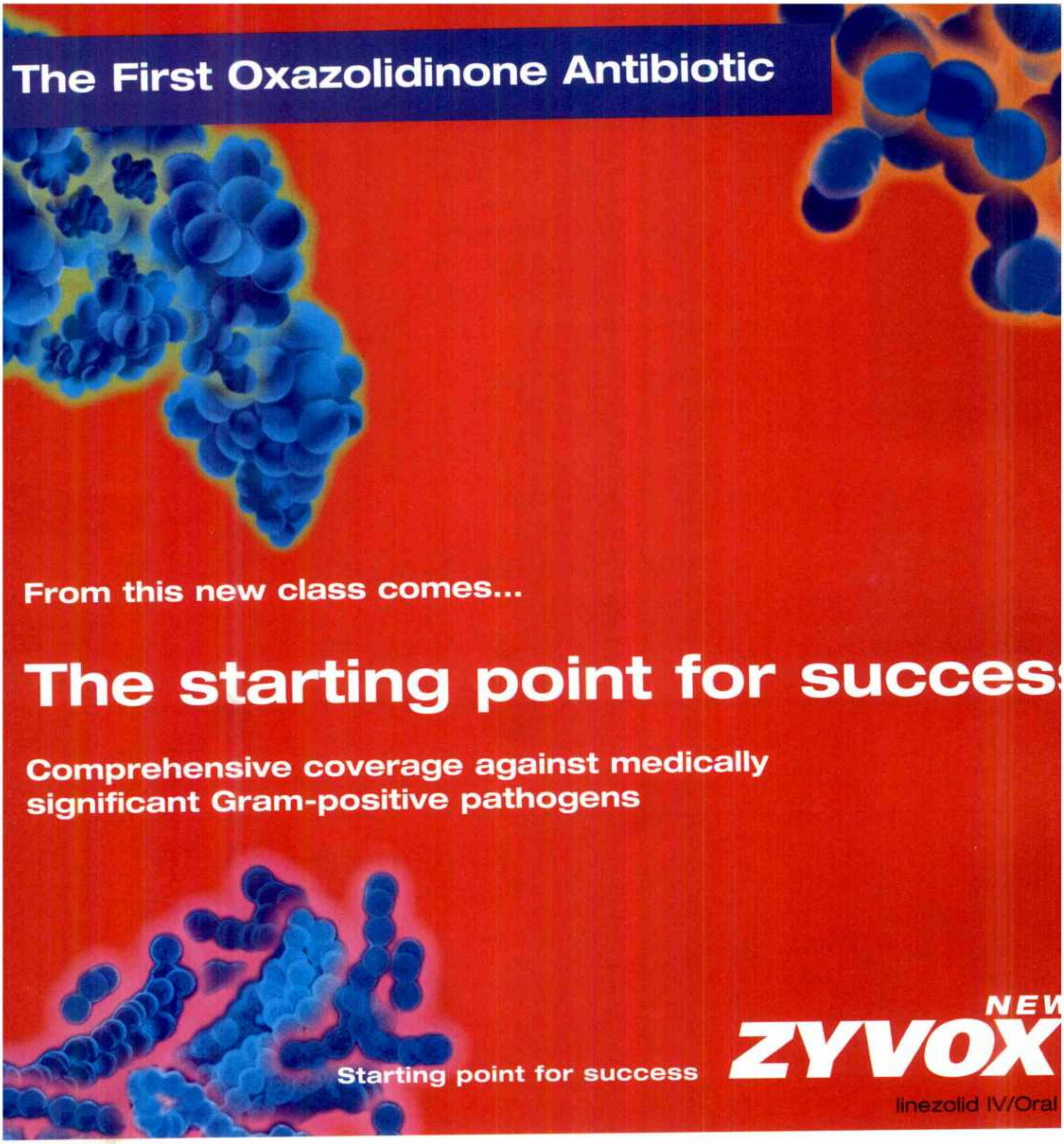
All blades and handles are manufactured in Sheffield, England

Swann-Morton®
PRECISION IN YOUR HANDS

Swann-Morton Limited,
Owlerton Green, Sheffield S6 2BJ, England.
Tel: 0114 234 4231 Fax: 0114 231 4966
e-mail:uksales@swann-morton.com
exportsales@swann-morton.com
www.swann-morton.com

CE
All medical devices are CE marked in accordance with the Medical Device Directive (93/42/EEC)

BS EN ISO 9001:1994
Certificate No: FM 14713



The First Oxazolidinone Antibiotic
From this new class comes...
The starting point for succes
Comprehensive coverage against medically significant Gram-positive pathogens
Starting point for success
NEW
ZYVOX
linezolid IV/Oral

PRESCRIBING INFORMATION See Summary of Product Characteristics before prescribing. **Zyvox 2 mg/ml Solution for Infusion (containing 2 mg/ml linezolid); Zyvox 600 mg Film Coated Tablets (containing 600mg linezolid). Indications:** Zyvox is indicated for the treatment of the following infections when known or suspected to be caused by susceptible micro-organisms: Nosocomial pneumonia, Community acquired pneumonia, Skin and soft tissue infections. **Dosage/Route of administration:** The solution for infusion should be administered over a period of 30 to 120 minutes. Dose (to be administered twice daily): Nosocomial pneumonia, Community acquired pneumonia 600 mg IV or orally. Skin and soft tissue infections 400 mg to 600 mg orally or 600 mg IV depending on clinical severity. Duration 10-14 days. No dose adjustment is required for elderly patients, patients with mild to moderate renal or hepatic insufficiency. Linezolid should be given after dialysis in patients receiving such treatment. Children: There are insufficient data to establish dosage recommendations. **Contraindications**: Patients hypersensitive to linezolid or any of the excipients. Patients taking any drug which inhibits monoamine oxidases A or B or within two weeks of taking any such drug. Linezolid should not be administered to patients with the following, unless there are facilities available for close observation and blood pressure monitoring: a) Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states or b) Patients taking any of the following medications: Serotonin re-uptake inhibitors, tricyclic antidepressants, directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents, dopaminergic agents, pethidine or buspirone.

Precautions: Linezolid should be used with special caution in patients with sever
or hepatic insufficiency and only when the anticipated benefit is considered to ou
the theoretical risk. Platelet counts and haemoglobin levels should be monit
patients who have pre-existing anaemia or thrombocytopenia, who are re
concomitant medications that may decrease haemoglobin levels, platelet cc
function, patients who have severe renal insufficiency, or those who receive mo
10-14 days of therapy. Pseudomembranous colitis has been reported with ne
antibacterial agents including linezolid. **Pregnancy**: Linezolid should not be used
pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the the
risk. **Driving**: Patients should be warned about the potential for dizziness whilst re
linezolid and advised not to drive if affected. **Side effects**: Headache, candidiasis
infection, eosinophilia, leucopenia, thrombocytopenia, abnormal liver functior
metallic taste, diarrhoea, nausea, vomiting, increased AST, ALT, LDH,
phosphatase, BUN, creatine kinase, lipase, amylase or non fasting glucose, dec
total protein, albumin, sodium or calcium, increased or decreased potass
bicarbonate, increased neutrophils, decreased haemoglobin, haematocrit or red bl
count, increased or decreased platelet or white blood cell counts. **Basic NHS cos**
Infusion 300 ml bag, 10 bags £445.00. Zyvox 600 mg tablet, 10 tablets £445.0
hospital cost: Zyvox Infusion 300 ml bag, 10 bags £335.00. Zyvox 600 mg
10 tablets £335.00. Marketing Authorisation Numbers: 300 ml bag: PL 003
600 mg tablet: PL 0032/0261 **Legal Classification**: POM **Further informa**
available from the Marketing Authorisation Holder: Pharmacia & Upjohn
Davy Avenue, Milton Keynes MK5 8PH. **Date of Preparation**: January 2001

PHARM

Contents

British Journal of Surgery

Volume 88, Issue 12, December 2001

Leading articles

1553 **Haemoglobin solutions in surgery**
G. J. Vlahakes
Short duration of efficacy remains a significant problem

1556 **Preoperative radiotherapy for rectal cancer**
C. A. M. Marijnen and C. J. H. van de Velde
A selective approach may yield significant benefit

Reviews

1558 **Immune therapy in inflammatory bowel disease and models of colitis**
B. Singh, F. Powrie and N. J. McC. Mortensen
Surgeons should be aware of the impact of immune therapy on inflammatory bowel disease

1570 **Suspected acute appendicitis: trends in management over 30 years**
P. F. Jones
Active observation is advocated

Randomized trial

1578 **Randomized clinical trial of patient-controlled *versus* fixed regimen feeding after elective abdominal surgery**
I. J. M. Han-Geurts, J. Jeekel, H. W. Tilanus and K. J. Brouwer
Patient-controlled feeding is safe and effective

Original articles

1583 **Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery**
J. I. Spark and D. J. A. Scott
The way an individual's neutrophils work may affect the rate of infection

1590 **Risk modelling study for carotid endarterectomy**
G. Kuhan, E. D. Gardiner, A. F. Abidia, I. C. Chetter, P. M. Renwick, B. F. Johnson, A. R. Wilkinson and P. T. McCollum
A new risk score using only three variables

1595 **Diverticular disease of the colon in Accra, Ghana (short note)**
B. N. Baako
Incidence related to age not diet

1596 **Plasma concentration of tissue inhibitor of matrix metalloproteinase 1 in patients with colorectal carcinoma**
N. Yukawa, T. Yoshikawa, M. Akaike, Y. Sugimasa, S. Takemiya, S. Yanoma, Y. Noguchi and Y. Takanashi
Correlates with invasion and metastasis

1602 **Salvage abdominal surgery in patients with a retained rectal stump after restorative proctocolectomy and stapled anastomosis**
H. Tulchinsky, J. S. McCourtney, K. V. Subba Rao, W. Chambers, J. Williams, K. H. Wilkinson and R. J. Nicholls
Anastomosis must be ileoanal

1607 **Impact of total mesorectal excision on the results of surgery of distal rectal cancer**
W. L. Law and K. W. Chu
Results from a single surgeon

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder

FELLOWSHIP OPPORTUNITY PEDIATRIC SURGICAL ONCOLOGY

The Department of Surgery at St. Jude Children's Research Hospital is offering a Fellowship in Pediatric Surgical Oncology. Eligible candidates should have completed either a general surgical residency program or a pediatric surgical training program or its equivalent. This Fellowship will be tailored to the needs of the candidate, but will include clinical training in the care of children with a variety of childhood malignancies as well as experience in clinical and basic research. The Fellowship will be for one year with an option to gain additional laboratory experience during a second year. Depending upon the experience of the candidate, arrangements can be made to spend three months of the first year participating in the care of adult surgical oncology patients with an emphasis on gaining additional experience in specific areas such as head and neck surgery and the management of adult sarcoma. Training in the use of advanced minimally invasive surgical techniques in children is also available depending upon the interest of the candidate.

Applicants should submit a curriculum vitae to: **Stephen J. Shochat, M.D., Chairman, Department of Surgery, St. Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38105. Ph: 901-495-2911; Fax: 901-495-2207.** EOE/MN/DN

www.stjude.org

INTERNATIONAL PERFIX PLUG HERNIA REPAIR WORKSHOP

Back to back with the XXIV International Congress of the European Hernia Society Meeting in Amsterdam (13-15 June 2002) this one day Royal College of Surgeons of England CME approved course provides delegates with an interactive overview of the PerFix plug hernia repair technique.

Chaired by Mr N Barwell (Truro, UK) live demonstrations (10 cases) of inguinal (indirect, direct and recurrent) and femoral hernia repair under general, epidural and local anaesthesia will be performed by:

Professor F E Isemer, Wiesbaden, Germany
Mr G Poston, Liverpool, United Kingdom
Mr B I Rees, Cardiff, Wales
Dr I Rutkow, Hernia Center, New Jersey, USA
Mr B M Stephenson, Newport, Wales

Course date: Monday 17 June 2002
Course fee: Consultants £150
Surgical trainees £100

For further information and application form please contact:

Mr B M Stephenson
Department of Surgery
Royal Gwent Hospital
Newport
S Wales, NP20 2UB

Tel: (44) 01633 234109
Fax: (44) 01633 234252
e-mail: Brian.Stephenson@gwent.wales.nhs.uk

Royal Society of Medicine Award Winner
"Telemedicine and Telecare in the NHS, 2000"

Surgical Training via Digital Satellite TV Free broadcasts to eligible sites for 2001/02

mrcsTV is a novel education and training programme for doctors studying for the examinations at any of the four Royal Colleges of Surgeons in England, Scotland and Ireland. Devised by Professor Andrew Kingsnorth FRCS, FACS and Surgeon Commander James Campbell FRCSEd, FRCS, **mrcsTV** is also relevant to doctors studying for similar qualifications around the world.

A series of 30 live TV programmes, each of 90 minutes duration, is broadcast on Friday lunchtimes from the University of Plymouth via high quality digital satellite TV to suitably equipped hospital education centres across the UK and Eire. These broadcasts cover a range of topics in modular format relevant to the MRCS syllabuses produced by the Royal Colleges.

- *learning in the workplace - saves travel time*
- *learning in the workplace - saves travel costs*
- *wider access to expert presenters*
- *opportunity to ask the experts questions*
- *access to video and photograhic content*
- *interaction with other surgical trainees*

For more information on how your hospital can connect to the **mrcsTV** network, call Tracey Honeychurch on 01752 763017 or e-mail her at: **tracey.honeychurch@phnt.swest.nhs.uk** or look at our web site: **http://www.mrcs.tv**

mrcsTV

Advanced Laparoscopic Course

Colchester General Hospital NHS

19-20 February 2002

This two day workshop will provide delegates with individual tuition including lectures, suturing and knot tying, as well as practical and operating sessions covering the latest techniques in laparoscopic surgery. All delegates will take part in the operative cases with Professor Roger Motson and Mr Donald Menzies.

Course content:

- Advanced techniques in laparoscopic cholecystectomy
  – dealing with difficult cases
- Detection of common bile duct stones and intra-operative cholangiography
- Laparoscopic common bile duct exploration
- Case demonstrations of the above and other advanced procedures including colonic resection, Nissen fundoplication and inguinal hernia repair

CME ACCREDITED

The course fee of £450.00 includes: overnight accommodation in Colchester, course handbook, laparoscopic common bile duct exploration videotape and course dinner.

For registration details please contact:

Miss Sarah Wilby
Colchester General Hospital
Telephone: (01206) 742448
Facsimile: (01206) 742030

Course approved by the AESGBI

Technical, administrative and financial support from

KeyMed
Specialised Services to Medicine & Industry

ETHICON ENDO-SURGERY
a Johnson & Johnson company

1613 **Systemic levels of glyceryl trinitrate following topical application to the anoderm do not correlate with the measured reduction in anal pressure**
M. Jonas, D. A. Barrett, P. N. Shaw and J. H. Scholefield
Marked variation in systemic levels and no correlation with side-effects

1617 **Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer**
J. Camilleri-Brennan and R. J. C. Steele
Quality of life improves with time

1623 **Function of a colonic J pouch continues to improve with time**
G. J. C. Harris, I. C. Lavery and V. W. Fazio
A review of 119 patients 5–9 years after operation

1628 **Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer**
M. L. George, A. S. K. Dzik-Jurasz, A. R. Padhani, G. Brown, D. M. Tait, S. A. Eccles and R. I. Swift
Selection for neoadjuvant therapy may be possible

1637 **Ileal neoappendicostomy for antegrade colonic irrigation (short note)**
P. Christensen, S. Buntzen, K. Krogh and S. Laurberg
What to do when the appendix is absent

1639 **Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection**
R. M. H. Roumen, G. P. Kuijt, I. H. Liem and M. W. P. M. van Beek
Strict criteria define the standard of care

1644 **Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer**
L. Bergkvist, J. Frisell, G. Liljegren, F. Celebioglu, S. Damm and M. Thörn
The first 498 operations done in Sweden

1649 **Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery**
T. M. Farrell, W. S. Richardson, T. L. Trus, C. D. Smith and J. G. Hunter
Atypical symptoms improve too

1653 **Correspondence**

1656 **Book reviews**

1658 **Scientific surgery**

1659 **Instructions to authors**

1661 **Author index**

1666 **Subject index**

1677 **Referee index**

0007-1323(200112)88:12;1-A

TO ADVERTISE IN THIS JOURNAL CONTACT:

Katrina Erskine

Tel: + 44 (0) 1865 206238 or Fax: +44 (0) 1 865 206189
Email: katrina.erskine@blacksci.co.uk

Or access our website for further information:
http://www.blackwell-science.com

Blackwell
Science

Blackwell Science Ltd, Osney Mead, Oxford, OX2 0EL, UK

Royal College of Surgeons of Edinburgh
EDINBURGH SURGICAL MASTERCLASS
UPPER GASTROINTESTINAL SURGERY
31 January – 1 February 2002
Chairman – Professor S M Griffin
Local Organiser – Mr Simon Raimes

Thursday 31 January
- **Assessment session**
- **Debate of the day** – 'Floppy Nissen fundoplication is the surgical treatment of choice for gastro-oesophageal reflux disease'
- **Operative surgery session**

Friday 1 February
- **Therapeutic session**
- **Debate of the day** – 'Self-expanding metal stents are the gold standard for the palliation of malignant dysphagia'

Faculty

Professor Derek Alderson
Mr C P Barham
Mr Geoffrey Clark
Mr R Hardwick
Mr John Anderson
Dr S V Baudouin
Professor S M Griffin
Professor Z H Krukowski
Dr Kelvin Palmer
Dr Ian Penman
Mr Simon Raimes
Mr R C Mason
Mr Simon Paterson-Brown
Mr S R Preston

The registration fee for the Masterclass is £295.00. The fee includes a copy of the relevant volume of the Companion to Specialist Surgical Practice (2nd Edition), all refreshments, lunches and Masterclass Dinner. For an application form and detailed programme, please apply to the Career Information Service. Tel: 44 (0) 131 668 9222.

EDINBURGH SURGICAL MASTERCLASSES- DIARY DATES

Hepatobiliary Surgery
21 & 22 March 2002
Chairman – Professor O James Garden
Local Organiser – Mr Rowan Parks

Endocrine and Breast Surgery
28 & 29 November 2002
Chairman – Professor J R Farndon
Local Organisers –
(Endocrine) - Mr Murat Aykol
(Breast) – Mr J M J Dixon

The Royal Surrey County Hospital
Minimal Access Therapy
training unit

LAPAROSCOPIC TRAINING COURSES

2002

BASIC LAPAROSCOPIC SKILLS
LAPAROSCOPIC CHOLECYSTECTOMY
GASTRIC REFLUX PROCEDURES
LAPAROSCOPIC COLORECTAL SURGERY
EXTRA PERITONEAL HERNIA REPAIR
ADVANCED LAPAROSCOPIC MASTERCLASS
INTRA CORPOREAL SUTURING TECHNIQUES

ALL COURSES INCLUDE:

LIVE SURGERY
LECTURES & DISCUSSION
HANDS ON TRAINING

International Faculty led by Professor Michael Bailey
Mr Amir Nisar, Senior Lecturer in Minimal Access Surgery

For further information contact:

Alison Snook
The Minimal Access Therapy Training Unit
The Royal Surrey County Hospital
Egerton Road
Guildford
Surrey GU7 5XX

Tel: 01483 303053 / Fax: 01483 406636
E-mail: alison@mattu.org.uk / www.mattu.org.uk (online registration)

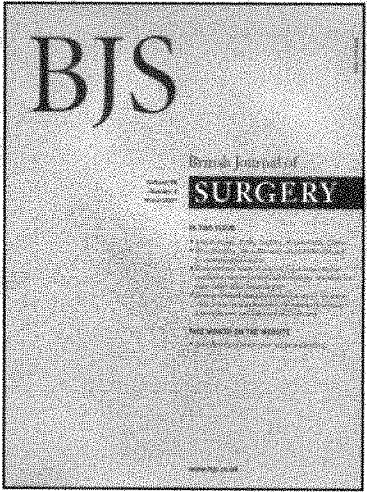
Blackwell
Science

BJS

British Journal of
SURGERY
now available online through
Blackwell *Synergy*

Visit *BJS* online FREE

Simply register at www.blackwell-synergy.com to:



- *Select* tables of contents emailed directly to your desktop, keeping you up-to-date with the latest publications in the field
- *Browse* through all tables of contents and article abstracts, and save favourites in your personal *Synergy* homepage
- *Search* by phrase, keyword, author, or title within full text articles for the information you need
- *Access* free sample issues

Subscribe to *BJS* and you will also be able to:

- *Choose* articles in full-text HTML, with embedded links, high quality figures and tables, or in PDF format, excellent for printing
- *Link* directly from references, authors and keywords to MEDLINE, and to cited articles in other journals
- *Save* articles to disk for your own research and for copying for course packs
- *Read* articles from all available online back volumes

If you are a member of the *Association of Surgeons, Surgical Research Society* or the *Association of Surgeons of the Netherlands*, you are entitled to access *BJS* online as part of your member benefits.

All qualifying members will be contacted by the Society or by Blackwell Science with instructions on how to access the journal on *Synergy*. If you are a member and would like help accessing *BJS* online, please contact Journal Customer Services on tel: +44 (0)1865 206126.

Your institution may already have a subscription to the online version of *BJS*. Simply ask your library administrator.

You can upgrade your Print Subscription to include the Online Version for just 10% extra, or subscribe to Online Only and save 10%.

Synergy
Blackwell
Online Journals

4th Whipps Cross
Oesophago-Gastric Symposium 'Meet-the-Experts'

_at_ The Royal College of Surgeons of England, Lincoln's Inn Fields, London

Thursday 31 January 2002

A One Day symposium on **Gastro-Oesophageal Reflux Disease (GORD)** for consultants and trainees in Gastroenterology and Gastrointestinal Surgery has been arranged. A proportion of patients with severe GORD are refered to hospital and stand to benefit significantly from an anti-reflux procedure. It is crucial that we are able to select these patients, select the appropriate procedure and perform the operation to the highest technical standards required to ensure a good long term quality of life. This fourth Whipps Cross Oesophago-Gastric Symposium will bring together a panel of expert international speakers at The Royal College of Surgeons of England in London to lead the discussions on:

- selecting patients for anti-reflux surgery,
- choosing the most appropriate procedure and
- agreeing the optimal techniques of anti-reflux surgery

Faculty

- Mike Bailey
- Bernard Dallemagne
- Tom Dehn
- David Evans
- Bob Heading
- Ziggy Krukowski
- Lars Lundell
- Bill Owen
- Paul Swain
- James Wellwood
- Marc Winslet

Discussion topics of GORD

- Physicianly thoughts
- Selecting patients for surgery
- Choosing the right procedure
- Quality of life after treatment
- What to do when all goes wrong
- Difficult cases discussion

Video presentations **with practical aspects of:**

- Gastroscopic anti-reflux procedures
- Nissen-Rosetti 360° posterior wrap
- Watson 180° anterior wrap
- Toupet 180° posterior wrap
- Dealing with large hiatal herniae
- Revisional anti-reflux surgery

Symposium organiser: Mr Abrie Botha, Consultant Surgeon, Whipps Cross Hospital

Fee: £65

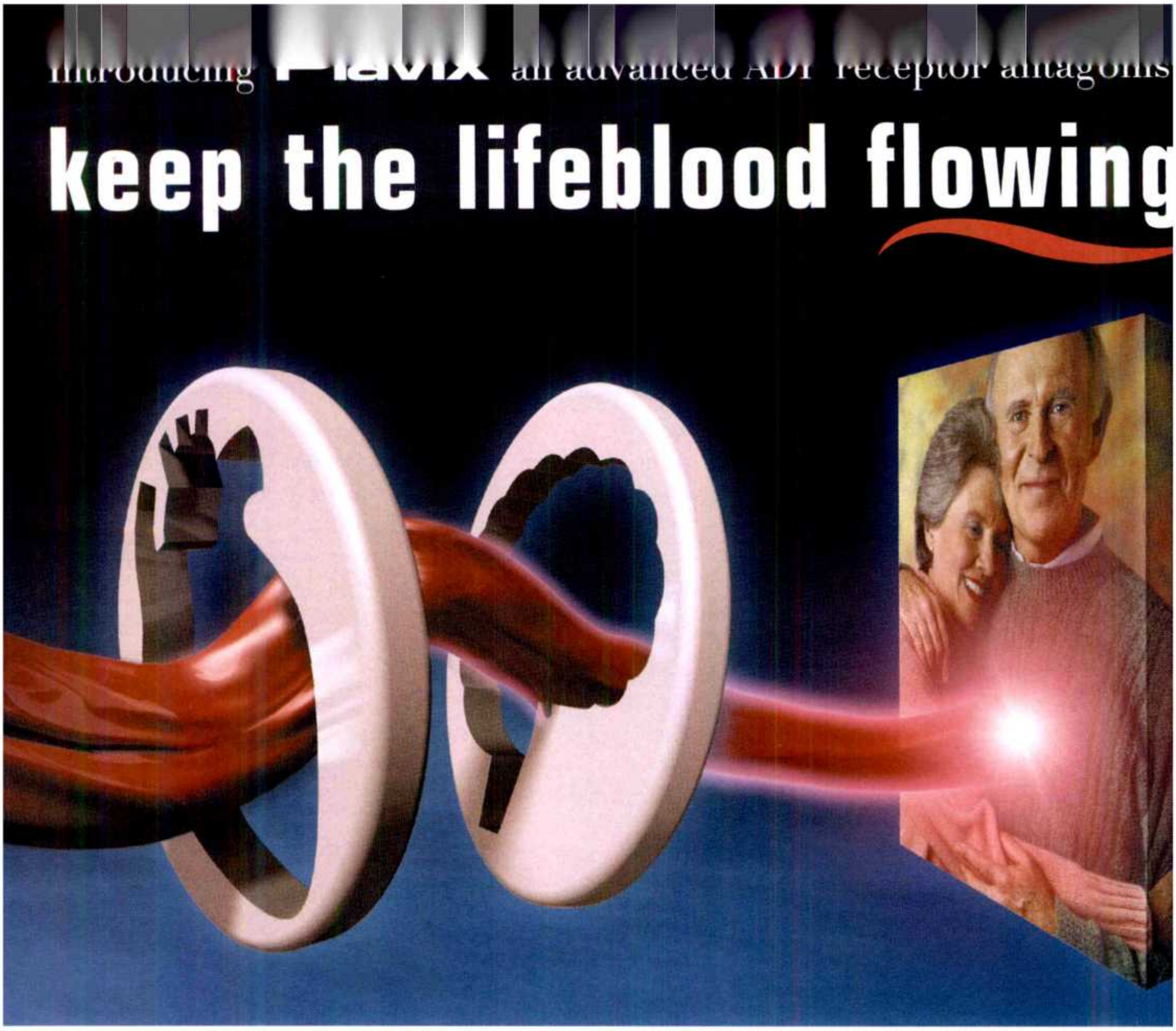
For application forms and enquiries contact:
Ms Maxine Levene, Secretary to Mr Botha,
Whipps Cross Hospital, Leytonstone, London, E11 1NR Phone/Fax: 020 – 8535 6656

CME accreditation has been applied for.

The Royal College of Surgeons of England

Whipps Cross
University Hospital

NHS


an advanced ADP receptor antagonis
keep the lifeblood flowin

Introducing PLAVIX - the first drug specifically designed for, and proven in, the prevention of further ischaemic events: MI, STROKE and VASCULAR DEATH.*

In a trial against aspirin in over 19,000 recent MI, recent ischaemic stroke and atherosclerotic PVD patients, PLAVIX was proven to be significantly more effective at reducing further events: MI, STROKE and VASCULAR DEATH.[1]*

*CAPRIE: comparison of efficacy of clopidogrel versus aspirin; Inclusion criteria: patients with ischaemic stroke (from 7 days to less than 6 months), MI (less than days) or established peripheral vascular disease; Endpoint: Combined endpoint MI, ischaemic stroke, vascular death for the overall population

Plavix®

clopidogrel 75mg

PREVENTING VASCULAR EVENT

sanofi~synthelabo

Bristol-Myers Squil

PLAVIX PRESCRIBING INFORMATION. PRESENTATION: Round, pink, film coated tablets containing 75mg clopidogrel (as the bisulphate). INDICATION: Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days), or established peripheral arterial disease. DOSAGE: Adults and elderly: 75mg as a single daily dose. Children and adolescents: Not recommended under 18 years. CONTRAINDICATIONS: Hypersensitivity to clopidogrel or excipients; severe liver impairment; active pathological bleeding; breast-feeding. WARNINGS: Due to the risk of bleeding and haematological disorders, blood cell count determination should be conducted where suspected clinical symptoms arise during treatment; caution in patients with lesions likely to bleed, particularly gastrointestinal and intraocular; renal impairment; hepatic disease. Not recommended during pregnancy. DRUG INTERACTIONS: Not recommended with warfarin. Caution when used with acetylsalicyclic acid, NSAIDS, heparin, thrombolytics, glycoprotein IIb/IIIa inhibitors. Blood cell count determination is required during first week of co-administration. SIDE EFFECTS: Haematological disorders including very rare cases of thrombotic thrombocytopenic purpura, very rare cas of severe thrombocytopenia, agranulocytosis, anaemia and aplastic anaemia / pancytoper haemorrhagic including serious bleeding such as skin bleeding, bruising, haemarthrosis, haematon eye bleeding, epistaxis, respiratory tract bleeding, haematuria and intracranial, gastrointestinal a retroperitoneal haemorrhage and haemorrhage of operative wound; gastrointestinal includ diarrhoea; very rare cases of renal disorders and abnormal creatinine levels; allergic disord including skin reactions, bronchospasm, angioedema, anaphylactoid reactions, fever, arthralgia a arthritis; very rare cases of taste disorders and confusion. LEGAL CATEGORY: POM. PRODU LICENCE NUMBER: EU/1/98/069/001a. MARKETING AUTHORISATION HOLDER: Sanofi Phar Bristol-Myers Squibb SNC. FURTHER INFORMATION IS AVAILABLE FROM: Sanofi-Synthela One Onslow Street, Guildford, Surrey, GU1 4YS. TEL: 01483 505515. FAX: 01483 5354 BASIC NHS PRICE: £35.31 for 28 tablets. DATE OF PREPARATION: September 20 Reference: 1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel vers aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-13

PLA 01/182

Leading article

Haemoglobin solutions in surgery

G. J. Vlahakes

Department of Surgery, Massachusetts General Hospital, 55 Fruit Street, BUL119, Boston, Massachusetts 02114–2696, USA
(e-mail: vlahakes.gus@mgh.harvard.edu)

Approximately 60 per cent of blood transfusions (30 million units annually, worldwide) are infused in conjunction with operative blood loss. Consequently, there exists an important place in surgery for safe and efficacious transfusion alternatives. Most recent progress in blood substitute development has been in the area of haemoglobin-based oxygen carrying (HBOC) solutions, several of which are currently in advanced clinical trials; they differ, in part, because their haemoglobin is derived from different sources.

Efficacy issues

It has been shown that HBOC solutions can carry the same amount of oxygen as blood and so, in experimental studies, it has been possible to achieve near-complete replacement of the autologous red cell mass using these materials[1]. After introduction of HBOC solutions into initial clinical trials, however, certain limitations emerged that influence how these solutions can be applied in clinical practice. Unpolymerized haemoglobin when infused has a short half-life of 6–8 h. Thus, with the exception of applications in which such an extremely short half-life is adequate (such as the acute stabilization of trauma), this type of low molecular weight HBOC preparation has limited clinical usefulness as a substitute for traditional blood transfusion. Other types of HBOC solution have been prepared by polymerization, most commonly with glutaraldehyde. This produces a family of polymers, and altering the polymerization process and/or selective molecular weight ultrafiltration can influence the molecular weight distribution. Typically, the average molecular weight of such preparations is 200 000–250 000 kDa.

Polymerization can increase half-life although it remains relatively short, especially compared with that of traditional red cell transfusion. Furthermore, in the plasma phase there is little methaemoglobin reductase activity and so HBOC solutions can undergo oxidation *in vivo* to methaemoglobin, which cannot carry oxygen[2]. The relatively short circulating half-life of free haemoglobin, even when polymerized, combined with spontaneous oxidation, results in a functional circulating half-life of approximately 24 h (*Fig. 1*). This important phenomenon and limitation in efficacy must be considered when seeking clinical applications for these materials.

Potential applications

Use as blood substitutes

In use as traditional blood replacement, the short duration of efficacy of HBOC solutions is a significant issue. In clinical trials in which these materials are being used instead of autologous red cell transfusion, the doses currently employed, combined with the short half-life, have produced limited efficacy in overall blood conservation. A possible exception is in their use in treating postoperative anaemia after cardiac surgery employing cardiopulmonary bypass. During the first 8–12 h after bypass, cardiac surgery patients

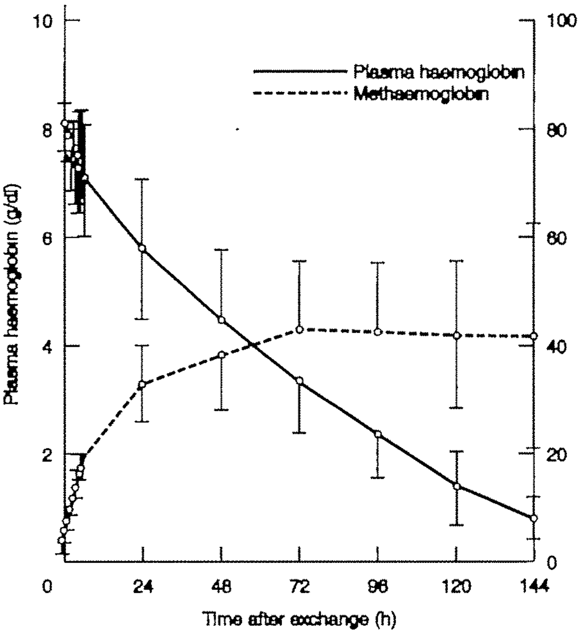


Fig. 1 Mean(s.d.) plasma haemoglobin and methaemoglobin levels following near-total blood exchange with a bovine-derived haemoglobin-based oxygen carrying (HBOC) solution in a conscious animal model. Note the conversion of up to 40 per cent of the infused HBOC product to methaemoglobin by 72 h. Reproduced with permission[2].

usually undergo rewarming, and arterial and venous vasodilation. This results in a volume requirement, and haemodilution occurs that produces a nadir in haematocrit within the first few postoperative hours. Transfusion decisions are generally made at around the time of this nadir[3]. In the days that follow a cardiac operation, as fluid is mobilized and excreted, some haemoconcentration occurs, producing a sharp rise in haematocrit by the fourth or fifth postoperative day. Patients having cardiac surgery may therefore benefit from a short-term 'oxygen transport bridge' until haemoconcentration occurs. Use of HBOC solutions is one possible means of achieving this, as suggested in a recent clinical trial[4].

Use in preoperative autologous donation

One useful technique that has permitted avoidance of allogeneic blood exposure in surgery is preoperative autologous donation. In some surgical settings, however, the acuteness of the situation or lack of physiological reserve may preclude such donation. HBOC solutions may be used in a novel way to permit extended, acute autologous blood donation immediately before surgery. In an experimental model, a haemoglobin-based blood substitute was used to achieve acute donation of approximately 70 per cent of the autologous red cell mass[5]. Because of the oxygen carrying capacity provided by the HBOC product, the high degree of removal of the autologous red cell mass was well tolerated in a subsequent experimental surgical stress. Following intraoperative blood loss, the autologous blood may be readministered.

Novel applications

Because of the low viscosity of these materials, and because they travel in the plasma phase, their behaviour in the microcirculation is different from that of erythrocytes. Studies of the microcirculation using vital microscopy have demonstrated that precapillary sphincters control the transit of erythrocytes, but do not necessarily completely exclude the plasma phase. So, if a cell-free, oxygenated haemoglobin solution is present in the plasma phase, it may reach target tissues with less local regulation than erythrocytes. The consequence of this has been studied experimentally. Using a needle oxygen sensor (Sigma-pO_2-Histograph KIMOC 6650, Eppendorf-Netherler-Hinz, Hamburg, Germany), Standl and colleagues demonstrated that the addition of even small amounts of HBOC solution into the circulation can substantially change local tissue oxygen tension[6], and that this effect operates even in the presence of arterial stenosis[7]. This suggests potential applications in the management of vaso-occlusive diseases, such as peripheral vascular disease producing non-healing leg lesions, and coronary ischaemia.

Issues and controversies in development of haemoglobin solutions

Free haemoglobin is known to possess high-affinity nitric oxide binding properties. This area has been explored for over a decade, and nitric oxide binding is thought to be the mechanism by which many HBOC solutions exert their so-called 'vasoconstrictor' effect[8]. In virtually every clinical study performed to date, some increase in systemic vascular resistance has been demonstrated. This effect is thought to result from an interaction of haemoglobin with nitric oxide, a concept that requires diffusion of haemoglobin through the endothelium to the interstitial space where the physiological effects of nitric oxide are considered to occur. While there may be some applications in which this is of benefit[9], initial concern was about possible deleterious effects. For instance it has been suggested that the vasoconstrictor effect may override or diminish any benefit from improved oxygen delivery. Consistent with this is the observation that when HBOC solution was administered in a shock model, higher lactate levels were observed following resuscitation[10]. Modifications to HBOC solutions may be required if such effects on vascular biology prove to have deleterious consequences in clinical applications. This is one of several important issues that are currently under investigation, but it is the short duration of efficacy of current HBOC preparations that remains the major limitation of these materials if they are to be used in applications similar to those of traditional blood transfusion.

References

1 Vlahakes GJ, Lee R, Jacobs EE Jr, LaRaia PJ, Austen WG. Hemodynamic effects and oxygen transport properties of a new blood substitute in a model of massive blood replacement. *J Thorac Cardiovasc Surg* 1990; **100:** 379–88.

2 Lee R, Neya K, Svizzero TA, Vlahakes GJ. Limitations of the efficacy of hemoglobin-based oxygen-carrying solutions. *J Appl Physiol* 1995; **79:** 236–42.

3 Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R *et al.* Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology* 1998; **88:** 327–33.

4 Levy JH, Goodnough LT, Greilich P, Parr G, Stewart RW, Gratz I *et al.* A room-temperature stable hemoglobin (HBOC-201) eliminates allogeneic red blood cell (RBC) transfusion in

post-operative cardiac surgery patients. *Circulation* 1998; **98**(Suppl I): I132(Abstract).

5 Slanetz PJ, Lee R, Page R, Jacobs EE Jr, LaRaia PJ, Vlahakes GJ. Hemoglobin blood substitutes in extended autologous preoperative blood donation: an experimental study. *Surgery* 1994; **115**: 246–54

6 Standl TG, Reeker W, Redmann G, Kochs E, Werner C, Shulte am Esch J. Haemodynamic changes and skeletal muscle oxygen tension during complete blood exchange with ultrapurified polymerized bovine haemoglobin. *Intensive Care Med* 1997; **23**: 865–72.

7 Horn E-P, Standl T, Wilhelm S, Jacobs EE, Freitag U, Frietag M *et al.* Bovine hemoglobin increases skeletal muscle oxygenation during 95% artificial arterial stenosis. *Surgery* 1997; **121**: 411–18.

8 Vogel WM, Dennis RC, Cassidy G, Apstein CS, Valeri CR. Coronary constrictor effect of stroma-free hemoglobin solutions. *Am J Physiol* 1986; **251**: H413–20.

9 Reah G, Bodenham AR, Mallick A, Daily EK, Przybelski RJ. Initial evaluation of diaspirin cross-linked hemoglobin (DCLHb) as a vasopressor in critically ill patients. *Crit Care Med* 1997; **25**: 1480–8.

10 Winslow RM, Gonzales A, Gonzales ML, Magde M, McCarthy M, Rohlfs RJ *et al.* Vascular resistance and efficacy of red cell substitutes in a rat hemorrhage model. *J Appl Physiol* 1998; **85**: 993–1003.

BJS impact factor

'The impact factor of a journal is probably the only quantitative way of assessing its worth and relevance to the academic community it serves'[1]. In some situations academic worth is measured using the bibliographies of individuals within departments and correlating these with cited source impact factors. The impact factor is the ratio of the total number of citations received in a given year to the articles published in the previous 2 years, to the total number of citable articles published by that journal in those 2 years.

The *BJS* impact factor has risen from 1·78 in 1992 to the latest rating in September this year of 2·94. *BJS* is second only to *Annals of Surgery* as a general surgical journal in worldwide rankings. *Annals of Surgery* scores 5·99 and, for comparison, the *New England Journal of Medicine* scores 29·51, *BMJ* 5·33, *American Journal of Surgery* 2·12 and *World Journal of Surgery* 2·02.

The editors wish to thank everyone who submits papers to *BJS*, those who bear rejection without complaint, and those who drive up our standards by their incisive and efficient refereeing.

J. R. Farndon
Editor

1 Taylor S. *The Impact Factor*. Oxford: Blackwell Publishing, 2001.

Leading article

Preoperative radiotherapy for rectal cancer

C. A. M. Marijnen* and C. J. H. van de Velde†

Departments of *Clinical Oncology and †Surgery, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands
(e-mail: velde@lumc.nl)

The mainstay of treatment of infiltrating rectal carcinoma is radical surgery, with or without sphincter preservation. While 15–50 per cent of patients will have a pelvic relapse after conventional surgery, two recent meta-analyses have demonstrated that radiotherapy reduces such local recurrence and might even improve survival[1,2]. In a recent multicentre trial[3], in which surgery and pathology were standardized for the first time, it was demonstrated that the introduction of total mesorectal or circumferential excision (TME) reduced pelvic relapse (8·2 per cent), compared with historical controls (22 per cent). With these excellent results for TME alone, the question arises whether adjuvant radiotherapy is necessary for all patients and, if so, when.

Timing

Should adjuvant radiotherapy be given before or after operation? For several indications there can be no discussion: the aim of downstaging or increasing the number of sphincter-saving procedures can obviously be achieved only by preoperative radiotherapy. Consequently, the discussion about preoperative or postoperative radiotherapy focuses on the prevention of local recurrence. Although traditional National Institutes of Health guidelines in the USA still recommend postoperative radiotherapy combined with chemotherapy, the evidence is contradictory. The only trial that has addressed the question compared short-term preoperative radiotherapy (5 × 5 Gy) with postoperative radiotherapy in patients with Dukes' stage B and C tumours. The results demonstrated the superiority of preoperative over postoperative radiotherapy, with local recurrence rates of 12 and 21 per cent respectively ($P = 0{\cdot}02$)[4]. Preoperative radiotherapy has several advantages in terms of compliance, duration of treatment, morbidity and financial cost. The appeal of postoperative radiotherapy is that the selection of patients to receive adjuvant treatment can be based on factors that are known to influence local recurrence. Although the balance between treatment burden and efficiency is in favour of preoperative radiotherapy, this lack of selectivity remains a matter that must be resolved.

Reduction of local recurrence

Over the past decade, preoperative radiotherapy has been given in a short-term scheme of 5 × 5 Gy followed by operation within 1 week with the aim of preventing local recurrence. Several trials of conventional surgery have shown improved local control with this scheme[4,5], with one study even demonstrating improved survival[6]. In the randomized trial of standardized TME, a decrease in local recurrence rate from 8·2 per cent in non-irradiated patients to 2·4 per cent in irradiated patients was observed[3], demonstrating that radiotherapy has a beneficial effect even in patients having TME.

Do all patients need preoperative radiotherapy?

Subgroup analysis in the above TME study[3] and in the Swedish Rectal Cancer Trial[6] has revealed that for proximal lesions and tumour node metastasis (TNM) stage I tumours radiotherapy has no significant influence on local recurrence. Consequently, the administration of preoperative radiotherapy for these subgroups in the absence of optimal preoperative staging is still open to debate. However, the relatively high frequency of local recurrence in patients who undergo an abdominoperineal resection suggests that radiotherapy must always be given in these cases.

Despite surgery and pathology being quality controlled in the TME trial, the proportion of patients with a positive circumferential margin was still 18 per cent; this increases the risk of both local and distant recurrence. An improvement in preoperative imaging to permit the reliable identification of patients who are at risk of circumferential margin involvement is clearly required. The value of preoperative radiotherapy in these patients, either alone or in combination with chemotherapy, merits further investigation. The ongoing Medical Research Council CR07 trial, which randomizes between preoperative radiotherapy and selective postoperative chemoradiotherapy, might provide part of the answer.

Downstaging and downsizing

Short-term preoperative radiotherapy yields excellent results in terms of local control, but is not the standard treatment for locally advanced tumours. These lesions require downstaging; this is not achieved with 5 × 5 Gy and a short interval between radiotherapy and operation[7]

To avoid short-term preoperative radiotherapy in patients with a locally advanced tumour, preoperative magnetic resonance imaging has been suggested for all patients with rectal cancer. Conventional radiotherapy with a total dose of 46–60 Gy, possibly combined with chemotherapy, is recommended for locally advanced lesions. To allow sufficient time for such tumours to reduce sufficiently in size, the interval between radiotherapy and operation needs to be at least 4 weeks. An ongoing Swedish study (L. Pahlman and B. Glimelius, unpublished data) is addressing the occurrence of downstaging after 5 × 5 Gy when surgery is postponed. Patients are randomized to a short (less than 1 week) or a long (4–6 weeks) interval between radiotherapy and operation.

In low rectal cancer, radiotherapy can be used to increase the safety of a sphincter-saving procedure by devitalizing tumour cells that might be left behind. Furthermore, it might facilitate this procedure in very low tumours by downsizing. A trial addressing the timing between radiotherapy (13 × 3 Gy) and operation for sphincter-saving procedures demonstrated a better clinical response in patients with a long interval (6–8 weeks) than in those with a short interval (1–2 weeks), but there was no difference in the proportion of sphincter-saving procedures (76 *versus* 68 per cent respectively; $P = 0{\cdot}27$)[8].

Side-effects

There has been concern about serious short- and long-term toxic effects of high fractional doses of preoperative radiation. In two trials that reported increased mortality rates short-term preoperative radiotherapy was administered using a suboptimal technique[5,9]. Several other trials have demonstrated that daily 5-Gy fractions can be given safely when an adequate treatment technique is employed[4]; this is so even when combined with TME[10]. Anastomotic leakage is not increased in patients undergoing TME after preoperative radiotherapy[10]. A twofold increase in perineal dehiscence is generally reported, both after short-term and after long-term preoperative radiotherapy. In the long term, small bowel complications are of most concern. However, the Uppsala trial[4] demonstrated that these occur more frequently in patients who have been irradiated after operation (11 per cent) than in those treated before operation (5 per cent).

Conclusion

Although optimized surgery results in a low rate of local recurrence, further improvement may be achieved by selective short-term preoperative radiotherapy, with an acceptable rate of morbidity. Further follow-up and analysis will refine the indications for this regimen in patients with operable rectal cancer.

References

1 Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. *JAMA* 2000; **284:** 1008–15.

2 Colorectal Cancer Collaborative Group. Meta-analysis of preoperative radiotherapy in rectal cancer. *Lancet* (in press).

3 Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.

4 Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; **36:** 564–72.

5 Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. *Cancer* 1995; **75:** 2269–75.

6 Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997, **336:** 980–7.

7 Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, Hermans J, van de Velde CJ, Leer JW *et al.* No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001, **19:** 1976–84.

8 Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C *et al.* Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999; **17:** 2396.

9 Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994; **30A:** 1602–6.

10 Marijnen CAM, Kapiteijn E, van de Velde CJH, Martijn H, Steup WH, Wiggers T *et al.* Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer. *J Clin Oncol* (in press).

Review

Immune therapy in inflammatory bowel disease and models of colitis

B. Singh, F. Powrie* and N. J. McC. Mortensen†

Nuffield Department of Surgery and †Department of Colorectal Surgery, John Radcliffe Hospital and *Sir William Dunn School of Pathology, Oxford, UK

Correspondence to: Mr B. Singh, Nuffield Department of Surgery, John Radcliffe Hospital, Oxford OX3 9DU, UK (e-mail: baljit.singh@nds.ox.ac.uk)

Background: A proliferation of animal models has not only improved our understanding of inflammatory bowel disease, it has also formed the basis of new treatment strategies.

Methods: A search was conducted using the National Library of Medicine for articles discussing immune therapies for inflammatory bowel disease. This was supplemented by findings from the authors' own laboratory.

Results: An overview of the different animal models is presented. These models are used to highlight the recent human trials of immune therapies. Potential future therapies are also discussed.

Conclusion: Immune therapies have altered the management of patients with inflammatory bowel disease. In future they will influence not only the indications for surgery but also its timing and outcome.

Based on a presentation to the American Society of Colorectal Surgeons tripartite meeting, Washington DC, USA, May 1999

Paper accepted 2 July 2001

British Journal of Surgery 2001, **88**, 1558–1569

Introduction

Inflammatory bowel disease develops in approximately 0·1 per cent of the Western population yet its aetiology and pathogenesis are incompletely understood. In recent years there has been a rapid expansion of animal models of the condition[1,2], resulting in new treatment protocols as well as potential future strategies[3]. Surgeons need to know about these developments as they will increasingly encounter patients who have been treated with first-line immunological agents, and these will ultimately alter the types of case referred to surgeons. These new treatments, however, have limitations and are not applicable to complications such as perforation, stricture or abscess. Furthermore, it may be possible to identify a cohort of patients in which surgical intervention should be the first line of treatment. An awareness of the complications of immune treatments as they relate to surgery is also important.

T-cell subsets and inflammatory bowel disease

CD4$^+$ T cells play a key role in controlling immune responses. From a common precursor they have the ability to differentiate into functionally distinct subsets[4] (*Fig. 1*). For example, T helper (Th) type 1 cells, which are important for macrophage activation, secrete interleukin (IL) 2, tumour necrosis factor (TNF) α and interferon (IFN) γ. In contrast, Th2 cells secrete IL-4 and IL-10[5], and provide help for antibody production. More recently, regulatory subsets have been described, Tr1[6,7] and Th3[8], which predominantly secrete IL-10 and transforming growth factor (TGF) β respectively, and can inhibit Th1 and Th2 responses. Both IL-12 and IL-18 have pivotal roles in the development of Th1 cells, whereas IL-4 has a similar role in Th2 development[9]. In addition, IL-4 is able to inhibit the expression of the β_2 subunit of the IL-12 receptor[10], thereby preventing a Th1 response, whereas murine IFN-γ (IFN-α in humans), the product of a Th1 response, stimulates β_2 expression.

In Crohn's disease there is strong evidence of a Th1-mediated pathogenesis[11–13]. Raised levels of IL-12 have been detected by reverse transcriptase–polymerase chain reaction in the colon and small intestine of affected patients[14]. This was not restricted to areas of inflammation and was also a feature of intestine of normal macroscopic and microscopic appearance. Similarly, increased levels of TNF-α have been detected in the stool of affected children[15]. More recently, the functional IL-12 receptor

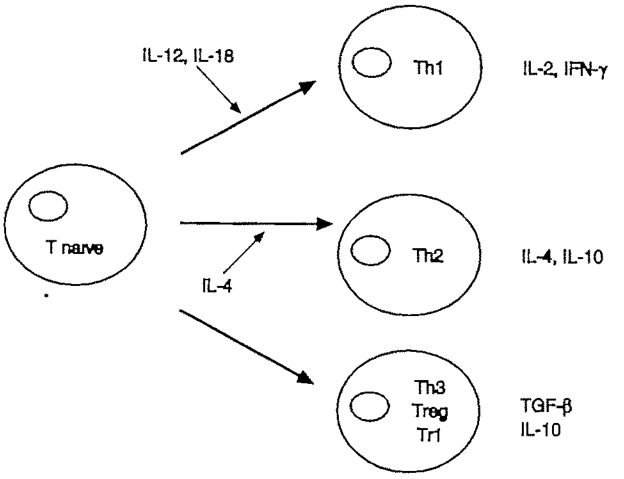


Fig. 1 CD4$^+$ T-cell subsets. These subsets are thought to originate from a common precursor T cell (T naive). The cytokines interleukin (IL) 12 and IL-18 are important in the generation of the T-cell subset referred to as T helper (Th) type 1, which is characterized by the production of IL-2 and interferon (IFN) γ. IL-4 plays a role in the development of the T-cell subset Th2, characterized by the production of IL-4 and IL-10. A third subset is the regulatory T cell. This may be a heterogeneous group, comprising subsets referred to as Th3, T regulatory (Treg) or Tr1. A feature of this group is its ability to produce either or both of the immunoregulatory cytokines IL-10 and transforming growth factor (TGF) β

subunit, β_2, has been found to be increased only at sites of active disease[16]. T cells, isolated from the lamina propria, secrete IFN-γ[17]. This is reduced when the cells are stimulated in the presence of an anti-IL-12 antibody[18]. Furthermore, raised levels of both mucosal IL-18 and the enzyme involved in converting IL-18 from the inactive secreted form to the active form, IL-1-converting enzyme, have been found in patients with Crohn's disease[19,20]. The significance of finding IL-18 is that it acts synergistically with IL-12 in the generation of Th1 cells.

Despite the evidence of a role for Th1 in Crohn's disease, support for a Th2 pathogenesis in ulcerative colitis is much weaker[21]. There are reports that lamina propria T cells secrete IL-5[17] and IL-4, but this is not a consistent finding. However, the presence of autoantibodies, such as anti-neutrophil cytoplasmic antibody, is suggestive of a Th2 pathogenesis. While Th1 cytokines do not appear to be raised in ulcerative colitis, there is no strong evidence for the presence of Th2 cytokines. These conflicting immunological findings are borne out in the paucity of animal models that are able to reproduce the pathological features of ulcerative colitis.

Animal models of inflammatory bowel disease

Many of the current immune strategies have been developed in animal models, of which the most widely used currently is the severe combined immune deficiency (SCID) model of colitis. Spontaneous models of inflammatory bowel disease are uncommon, the most studied being the cotton-top tamarin model[22,23]; these primates develop a colitis similar to ulcerative colitis. Strains of mice that develop a self-limiting form of right-sided colitis are the C3H/HeJBir[24] and the senescence-accelerated mouse P1/Yit (SAMP)[25]. Furthermore, CD4$^+$ T cells isolated from C3H/HeJBir mice are reactive to the normal gut flora[26] and can transfer colitis to immune-deficient mice. Chemically induced models of colitis can be produced by rectal instillation of trinitrobenzene sulphonic acid (TNBS)[27,28], acetic acid or oxazolone[29]. Oxazolone causes mice to develop features of ulcerative colitis, with raised levels of IL-4. Intramural injection of bacterial cell wall content[30] can also produce granulomatous changes in bowel.

Immune models form by far the largest group – one that has been expanding rapidly[31]. It is now possible to generate animals with a single deletion of a target gene (knockout animals) or increased expression of a particular gene (transgenic animals)[32]. Most of these manipulations have been carried out in mice, which has also allowed the study of candidate genes in inflammatory bowel disease. Animal models in which there is a defect in the epithelial barrier proteins, N-cadherin[33] or trefoil factor[34], develop inflammatory bowel disease. This is thought to allow enteric bacteria to trigger an immune response[35]. Deletion of either the cytokines IL-10 (IL-10$^{-/-}$)[36] and IL-2 (IL-2$^{-/-}$)[37] or their receptors, CRFB4$^{-/-}$[38] and IL-2Rα$^{-/-}$ respectively, also results in colitis. Furthermore, a murine model[39] in which a stable form of the TNF-α messenger RNA (mRNA) is expressed develops arthritis and granuloma formation in the terminal ileum. These findings support a major role for IL-10 and TNF-α in the pathogenesis of Crohn's disease[40]. T-cell receptors (TCRs) play a similar role in the development of colitis. TCR-α$^{-/-}$ mice, in which the α chain of the TCR is deleted, develop mucosal inflammation similar to that of ulcerative colitis. This is characterized by a Th2 cytokine profile and the presence of autoantibodies[41–43]. If these mice undergo an appendicectomy when 1 month old, the incidence of colitis is reduced dramatically[44].

The SCID model of colitis (*Fig. 2*)[45,46] is one of the most widely used immune models of inflammatory bowel disease. In this model transfer of a subpopulation of CD4$^+$ T cells, CD45RB^{high}, from an immunocompetent mouse to an immunodeficient animal (SCID or RAG$^{-/-}$) leads to a Th1-mediated colitis within 6–8 weeks, with extraintestinal

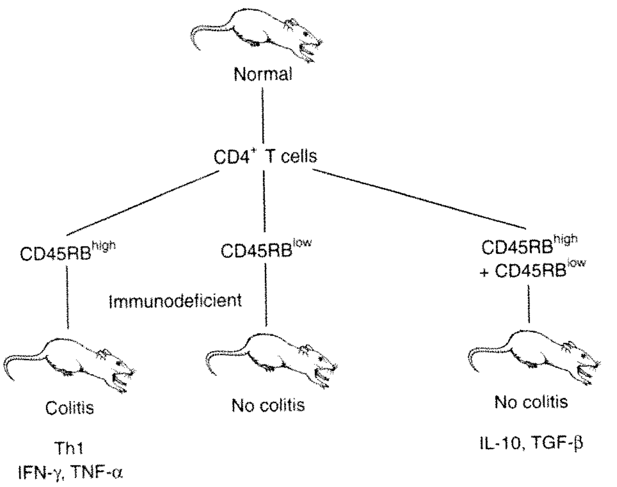


Fig. 2 The severe combined immune deficiency (SCID) model of colitis. CD4$^+$ T cells from the spleen of an immunocompetent mouse, labelled with an antibody to CD45RB, can be sorted according to high or low expression of this surface antigen. Transfer of CD4$^+$ CD45RB^{high} T cells to an immunodeficient mouse results in colitis which is characterized by a T helper (Th) type 1 cellular immune response with raised levels of interferon (IFN) γ and tumour necrosis factor (TNF) α. Transfer of the reciprocal population, CD4$^+$ CD45RB^{low} T cells, does not result in colitis. Furthermore, transfer of the CD4$^+$ CD45RB^{low} T cells with the CD4$^+$ CD45RB^{high} T cells prevents the development of colitis. This protection is dependent on interleukin (IL) 10 and transforming growth factor (TGF) β

manifestations involving the liver, skin and lungs[47]. In addition, transfer of the reciprocal population, CD45RB^{low}, with the pathogenic CD45RB^{high} prevents colitis. This model has helped to define the role of regulatory T-cell populations and inflammatory cytokines in inflammatory bowel disease[48] and, in particular, anti-TNF-α treatment. Further work has shown that the regulatory population is contained within the CD4$^+$ CD25$^+$ CD45RB^{low} population[49]. In experiments where CD25$^+$ T cells are depleted, mice develop autoimmune diseases such as diabetes, gastritis and thyroiditis[50].

Immune targets

The extensive number of animal models has highlighted potential immune targets. These can be at the level of the epithelial barrier or the enteric flora. Further targets are the co-stimulatory molecules involved in T-cell activation. Downstream targets include the proinflammatory Th1 cytokines, such as TNF-α and IL-12, generated following T-cell activation, or the nuclear factors involved in the transcription of these cytokines. A novel target is the enzymes involved in cytokine activation, such as TNF-α-converting enzyme, which converts TNF-α into its active form. While anti-TNF-α treatment has entered clinical practice, enzyme inhibitors would avoid many of the adverse effects associated with such antibody treatment. Other potential targets are the molecules involved in T-cell homing to the lamina propria.

Alternatively, regulatory cytokines, of which IL-10 has already entered into clinical practice, can downregulate the immune response. A potent strategy is to use regulatory T cells[51], which have been postulated to control the function of human T cells[52] reactive to enteric bacteria. This review discusses the targets of immunomodulators as well as the current immune strategies. It highlights immune targets, identified in animal models, that may become the basis of future treatments.

Steroids are commonly used in the treatment of inflammatory bowel disease. They reduce activation of macrophages, antagonize the effects of IFN-γ and prevent effective presentation of antigen by antigen-presenting cells. This accounts for their immunosuppressive effect. In contrast, immunomodulators, such as the macrolides cyclosporin A and tacrolimus (FK506), bind to intracellular receptors that are then able to inhibit the function of calcineurin. The end result is to prevent the activation of genes involved in T-cell proliferation, such as IL-2. Alternatively, azathioprine and its metabolite 6-mercaptopurine are purine analogues that, when incorporated into DNA, prevent T-cell proliferation. Similarly, methotrexate, a folic acid antagonist, also inhibits cell proliferation. These treatments have a non-specific effect on the immune system whereas current immune strategies are aimed at a specific target.

Current immune therapies

Tumour necrosis factor *α*

TNF-α is a cytokine produced by T cells and macrophages. It is secreted in an inactive form requiring activation by a metalloproteinase, TNF-α-activating enzyme. Its actions include activation of macrophages, increasing expression of adhesion molecules and the production of inflammatory cytokines. In the SCID model of colitis, continuous treatment with a TNF-α antibody prevented colitis[53] whereas treatment for 2 weeks was ineffective. On cessation of anti-TNF-α treatment colitis occurred within 4 weeks.

There have been several human trials showing the success of anti-TNF-α treatment in patients with Crohn's disease[54,55]. The antibody most commonly used has been infliximab (cA2 or Remicade®; Schering-Plough, Welwyn Garden City, UK), a monoclonal mouse–human chimaeric antibody immunoglobulin (Ig) G_1 against TNF-α. The earliest report involved a single infusion of infliximab, 10 mg/kg, in a group of ten patients with Crohn's disease involving the colon and/or terminal ileum who were unresponsive to steroids[56]. The effect was dramatic, with an improvement, as scored by colonoscopic findings and the Crohn's disease activity index (CDAI), occurring in eight of the ten patients 4 weeks after the initial infusion. The mean CDAI decreased from 257 before treatment to 79 at 4 weeks. Similarly, colonoscopy showed healing of nearly all the ulcers. The response also correlated with a normalization of inflammatory markers such as C-reactive protein level and erythrocyte sedimentation rate.

In a large randomized clinical trial[57], 108 patients with moderate to severe Crohn's disease were treated with a single infusion of infliximab of either 1, 5, 10 or 20 mg/kg; other drug treatments were left unchanged. Interestingly, response (defined as a reduction of the CDAI to less than 70) did not correlate with dosage. The highest response was noted in patients treated with 5 mg/kg and the response corresponded to a decrease in the Crohn's disease endoscopic index of severity (CDEIS)[58]. Histologically, the effect of cA2 was to reduce the cellular infiltrate and downregulate expression of adhesion molecules[59], but crypt architecture was still distorted despite treatment. After a single dose of anti-TNF-α, 33 per cent of patients had complete remission, as defined by a CDAI of less than 150. However, at 12 weeks after infusion this fell to 24 per cent, compared with 8 per cent in the placebo group. This again seems to correlate with the findings in the SCID model, with treatment having no lasting effect. Another consequence of treatment is that colonic strictures are prone to develop at sites of previous ulceration. In most cases management is by repeated dilatation[58]. This effect has been attributed to the rapid healing response rather than a direct action of anti-TNF-α.

Retreatment with anti-TNF-α is also effective. Patients who had responded to an initial infusion of infliximab were subsequently randomized to receive four further infusions of 10 mg/kg or placebo[60]; 66 per cent of the former group had a clinical response at 44 weeks, compared with 35 per cent in the placebo group. Anti-TNF-α treatment seems to be successful but repeated courses are needed to maintain long-term remission, and this has cost implications. Despite the effectiveness of anti-TNF-α, a subgroup of patients fails to respond to treatment. A possible explanation for this lies in a recent finding that Crohn's disease can be subdivided according to the level of serum perinuclear antineutrophil cytoplasmic antibody and antibodies to *Saccharomyces cerevisiae*[61], which correlate with the onset and severity of disease. These antibodies may be useful in predicting the likely response to anti-TNF-α treatment.

Anti-TNF-α treatment seems also to be effective in patients with Crohn's disease who have abdominal or perianal fistulas[62]. In contrast to Crohn's colitis, the initial treatment of fistulas comprised three infusions of infliximab. Response was impressive, with 55 per cent of patients treated with 5 mg/kg infliximab having complete closure of the fistula, compared with 13 per cent in the placebo group. Closure of fistulas did not correlate with dosage; only 38 per cent closure occurred in the group receiving 10 mg/kg infliximab. However, as in the case of colitis, healing was not permanent, with a median duration of only 3 months. A criticism of this study is the small number of abdominal fistulas (only seven of 56) in the treated group. Infliximab has also been successful in treating patients who developed signs of Crohn's disease following an ileoanal pouch procedure[63].

A complication of using the chimaeric cA2 is the development of autoantibodies against the murine component (human antichimaeric antibodies), which may lead to delayed hypersensitivity reactions. This seems to be more common if the time lapse between the first and second infusion is years rather than months. Such delayed hypersensitivity reactions can be reduced by concurrent use of immunomodulators. An alternative strategy is to use a completely humanized anti-TNF-α antibody, CDP-571 (IgG_4). This has also been successful in the treatment of Crohn's disease[64] and allowed patients with active disease to be weaned off steroids. However, a significant difference between infliximab and CDP-571 is the inability of the latter to activate complement, which may reduce its potency. The binding of cA2 to cell surface TNF-α allows these cells to be either lysed by complement or phagocytosed by macrophages. Long-term studies will determine whether these differences manifest themselves in altered immune response rates. There have been several documented cases of lymphoma following the use of cA2. Three cases have been reported in patients with Crohn's disease, two of non-Hodgkin's and one of Hodgkin's lymphoma[65]. This may be a casual association or related to the use of other immunosuppressants, such as cyclosporin or methotrexate, used in conjunction with cA2[66].

Despite the effectiveness of anti-TNF-α in Crohn's disease, its role in ulcerative colitis remains to be determined. It also remains to be seen whether anti-TNF-α treatment has a role in delaying or even preventing surgery in patients with Crohn's disease who have a single isolated involvement of the bowel. On the other hand, anti-TNF-α may be used as a preoperative adjunct to reduce the amount of resected bowel, particularly in patients with short bowel syndrome. Anti-TNF-α has not been evaluated in patients with Crohn's rectovaginal or enteroenteric fistula. It is also intriguing to speculate that anti-TNF-α may be effective in fistulas caused by conditions other than inflammatory bowel disease.

In the current climate of careful costing, an argument against using anti-TNF-α treatment is its expense and the need for further infusions to maintain remission. Other strategies employed to inhibit TNF-α include use of the controversial drug thalidomide and TNF-α receptor fusion proteins[67]. Thalidomide increases the rate of degradation of the mRNA for TNF-α, and initial reports describe encouraging results in patients with Crohn's disease[68,69]. However, the past history of this drug has understandably led to its cautious introduction. TNF-α receptor fusion proteins have proven successful in treating patients with rheumatoid arthritis. They consist of a TNF-α receptor, p75, which is able to bind to soluble TNF-α but lacks the ability to transmit a signal.

Interleukin 10

This cytokine plays an important role in regulating immune responses[70] by inhibiting both activated T cells and matrix metalloproteinases[71]. IL-10 can also reduce expression of co-stimulatory molecules, CD80 and CD86, on antigen-presenting cells and thereby cause a reduction in T-cell priming. In animal models it has a protective effect against the development of colitis[72]. In the SCID model of colitis, daily treatment with IL-10 prevents colitis[53]. Indeed, CD45RB$^{\text{low}}$ regulatory T cells are dependent of IL-10[73] as their protective effect is absent when they are isolated from IL-10$^{-/-}$ mice. This cytokine also prevents colitis in the TNBS model[74] and a similar rat model of colitis[75]. In the former, the IL-10 gene was administered in an adenovirus vector rather than as daily injections of recombinant IL-10, ensuring higher, more consistent, concentrations. Similarly, neutralizing IL-10 with an anti-IL-10 receptor antibody[73] also abrogates the protection by wild-type CD45RB$^{\text{low}}$ cells.

The results of IL-10 treatment in Crohn's disease have been more variable. Patients with mild to moderate disease[76] and not taking steroids had a beneficial effect with subcutaneous IL-10. In this trial an intermediate dose of 5 µg/kg, given daily for 28 days, led to remission (CDAI less than 150) in 23·5 per cent of patients, compared with 0 per cent in the placebo group. This was accompanied by endoscopic healing. Furthermore, patients with chronic active Crohn's disease[77], unresponsive to steroids, also had clinical improvement with subcutaneous IL-10 (decrease in CDAI to 100 or less), but remission was not induced. This clinical response, maximal at 8 µg/kg daily, was noted only after correcting for the CDAI, because IL-10 was associated with a decrease in the haematocrit. Again, the effect was not related to dosage as it decreased with the highest concentration, 20 µg/kg daily. This reduction in response has been attributed to a stimulatory effect of IL-10 on lymphocyte-produced inflammatory cytokines, which occurs only at high doses.

The side-effects of IL-10 include fever, arthralgia, headache, lymphopenia and a decrease in platelet numbers. In addition, daily subcutaneous administration makes it a cumbersome treatment, unsuitable in clinical practice. Intravenous IL-10 is also effective, but again needs to be administered on a daily basis[78]. It seems that IL-10 is effective in a subgroup of patients with mild to moderate Crohn's disease. Animal studies suggest only a short-term effect of IL-10 treatment (hence the need for repeated administration), but an advantage of using a naturally occurring cytokine is the reduced risk of developing autoantibodies.

Interleukin 11

IL-11 is made by bone marrow stromal cells and has been shown to prevent colitis in the TNBS model. One of the proposed mechanisms of action is to increase the mucosal integrity of the gastrointestinal barrier. Another possibility is that it modifies the transport of ions across the epithelium into the lumen[79]. IL-11 was initially used in patients following chemotherapy because of its thrombocytic potential. There has been a limited number of human trials using IL-11. Patients with active Crohn's disease, maintained on steroids or 5-aminosalicylate, had a beneficial effect with subcutaneous injections of IL-11[80]. The greatest response (42 per cent), defined as a decrease in the CDAI of more than or equal to 100, occurred at 16 µg per kg per week, given in five divided doses, compared with 7 per cent in the placebo group. A similar effect was observed in patients with Crohn's disease who were not taking steroids. A common side-effect of treatment is thrombocytosis; this can be reduced by giving divided doses of IL-11.

Adhesion molecules

Once CD4$^+$ T cells are activated, they have the ability to home to the gut. The mechanism by which this occurs involves specific gut-homing molecules, present on T cells, such as the integrin $\alpha_4\beta_7$. These bind to their co-receptors found on gut mucosa (mucosal addressin cell adhesion molecule 1) and gut endothelium (vascular cell adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1)[81].

In the cotton-top tamarin model of colitis, daily treatment for 8 days with a mouse–human chimaeric antibody to $\alpha_4\beta_7$ (Act-1) improved clinical and histological signs of colitis[82]. Similar treatment has also been successful in the SCID model of colitis. There have been some encouraging reports using an antibody to α_4 Natalizumab (Antegren; Elan Pharma, Letchworth, UK), with specificity to $\alpha_4\beta 1$ and $\alpha_4\beta_7$, in patients with Crohn's disease. In a small trial involving 30 patients a single infusion resulted in a 39 per cent remission rate in the treated group ($n = 18$) *versus* 8 per cent in the placebo group. However, the long-term response needs to be assessed as well as retreatment aspects.

An alternative strategy is to inhibit the interaction between the T cell and vascular endothelium. In this regard, potential targets are ICAM-1 and VCAM-1. Instead of an antibody to ICAM-1, a nucleotide sequence (antisense) that prevents the transcription of ICAM-1 has been successful in Crohn's disease. In this trial[83] involving 20 patients, seven of 15 treated patients attained remission, compared with one of five in the placebo group. This effect was long lasting as five of the seven patients were still in remission 6 months later. However, a criticism of the trial is the small numbers involved.

Potential immune targets and therapies identified in animal models

Co-stimulatory molecules

As our understanding of immune regulation in the intestine increases, the possibility of newer and more specific treatments begins to emerge. It is clear that T-cell activation is a critical step in development of colitis (*Fig. 3*). The current view is that T cells require two signals to become activated. The first signal is delivered by the peptide–TCR interacting with the major histocompatibility complex (MHC) present on antigen-presenting cells; the peptide may be an autoantigen or part of the normal gut flora. The second signal involves a co-stimulatory molecule present on antigen-presenting cells. The list of co-stimulatory molecules is extensive, and precisely how they all interact to determine T-cell function is not clear. However, modulation of T-cell co-stimulation has been shown to lead to a state of T-cell tolerance.

One particular molecule, which may be a potent target, is CD40 ligand (CD154; CD40L). This is found predominantly on activated CD4$^+$ T cells and interacts with the co-stimulatory molecule CD40, which is expressed on B cells, antigen-presenting cells and the endothelium. A key result of interaction between CD40 and CD40L is the generation of IL-12, which, as noted above, has a crucial role in the generation of Th1 cells. In patients with inflammatory bowel disease increased numbers of T cells expressing CD40L have been detected in the lamina propria[84,85]. These cells are capable of producing IL-12 when stimulated by resident macrophages. It is known that mice that overexpress CD40L (CD40L transgenic) develop colitis, and so it seems plausible that antibodies against CD40L may have a therapeutic role.

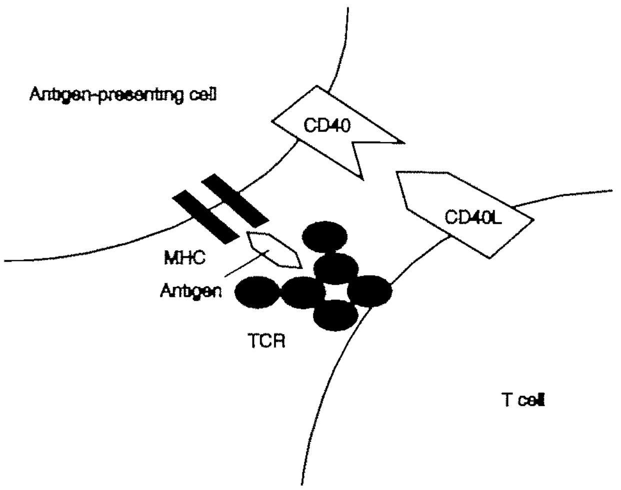


Fig. 3 The two-signal model for T-cell activation. The first signal is engagement of the major histocompatibility complex (MHC), present on antigen-presenting cells, in association with antigen and the T-cell receptor (TCR) The second signal comes via co-stimulatory molecules, of which there are several. In the figure this is illustrated by the co-stimulatory interaction of CD40 ligand (CD40L), present on activated T cells, and CD40, present on antigen-presenting cells

In the TNBS model, anti-CD40L antibodies (MR1) prevent colitis[86]. This is also observed in the *SCID* model, where even delayed treatment reduces the severity of colitis[87,88]. These observations illustrate the potential for anti-CD40L treatment. This has already been applied in the field of transplantation, where such treatment is effective in preventing rejection when completely MHC-mismatched renal allografts are transplanted in primates[89]. However, MR1 treatment is associated with thromboembolic complications. If the treatment of inflammatory bowel disease parallels the developments in transplantation, combined therapies may be more effective. One example is to target two or more co-stimulatory pathways, for example anti-CD40L and a cytotoxic T lymphocyte-associated antigen (CTLA) 4 fusion protein. The latter molecule is able to block interaction with the co-stimulatory molecules B7.1 and B7.2, present on antigen-presenting cells. There remain several more co-stimulatory molecules that may prove of equal interest. Some are expressed by activated dendritic cells, such as OX40 ligand (CD134L), and targeting these may be worthwhile in view of the importance of dendritic cells in co-ordinating inflammatory responses.

Interleukin 12 and interleukin 18

One of the results of the interaction between T cells and antigen-presenting cells is the generation of cytokines, which in the case of Crohn's disease include IL-12. Transmural colitis develops in mice in which the effects of IL-12 are enhanced, for example by overexpression of an IL-12 signalling molecule, signal transducer and activator of transcription (Stat) 4[90]. Similarly, T cells from Stat-4 knockout mice fail to induce colitis when transferred to *SCID* mice[91]. IL-12 is not only involved in the differentiation of Th1 cells but also increases the level of stromelysin 1, a tissue matrix metalloproteinase, which leads to tissue degradation[92]. As there are numerous co-stimulatory molecules, blockade of only one or two may be ineffective and another target worth considering is the resulting product, IL-12. IL-12 targeting may be achieved by at least two mechanisms, an antibody or a natural IL-12 antagonist.

Anti-IL-12 treatment is effective in the TNBS model of colitis, where it can reverse even established colitis[93]. Another mechanism of action of anti-IL-12 treatment is the programmed cell death, apoptosis, of inflammatory cells in the colonic lamina propria[94]. In IL-$10^{-/-}$ mice, anti-IL-12 treatment is also able to reduce the severity of colitis[95]. An alternative strategy is to use the natural antagonist, p40 dimers. It is known that IL-12 exists as a heterodimer, composed of subunits p35 and p40. When dimers of p40 are used, this constitutes an effective natural antagonist, which avoids the problems of delayed hypersensitivity reactions commonly encountered with chimaeric antibodies.

Other potential targets are cytokines that act synergistically with IL-12. For example, an effective combination treatment may involve the addition of anti-IL-18 antibodies. This cytokine synergizes with IL-12 in the generation of a Th1 response. Two other cytokines that are produced by intestinal epithelial cells are IL-15[96] and IL-7. These enhance the action of IL-12 in producing IFN-γ[97]. IL-7 transgenic mice develop a colitis resembling ulcerative colitis[98], and so this cytokine is a potential target, in combination with IL-12, for treating inflammatory bowel disease.

Interferon γ, interleukin 6 and interleukin 16

In the *SCID* model of colitis the most effective treatment is anti-IFN-γ[53]. This is not only effective when given continuously: two doses of anti-IFN-γ prevented colitis in four of seven mice, whereas a similar dose of anti-TNF-α failed to prevent all the mice developing colitis. It therefore seems reasonable to consider anti-IFN-γ treatment for inflammatory bowel disease. This treatment has already been employed in patients with chronic hepatitis. However, one concern is the long-lasting effect of IFN-γ blockade, particularly as IFN-γ is required as part of the innate immune response against foreign pathogens. In addition, neutralizing IFN-γ may be compensated for by a switch to TNF-α production.

IL-6 is found in increased levels in the colonic mucosa of patients with Crohn's disease. This cytokine binds to its soluble receptor and prevents the normal death cycle of activated T cells. In the SCID and TNBS models, and IL-$10^{-/-}$ mice blockade of IL-6, anti-IL-6 receptor antibodies prevent colitis[99,100]. Anti-IL-16 is also effective in preventing colitis in the TNBS model[101].

Regulatory T-cell subsets and cytokines

The cytokines IL-10 and TGF-β play a role in the development and function of regulatory T cells. The former agent has already entered clinical practice and the latter is known to have anti-inflammatory properties in some systems. In the SCID model of colitis, regulation of the pathogenic $CD4^+$ $CD45RB^{high}$ population by $CD4^+$ $CD45RB^{low}$ T cells is dependent on TGF-β[102]. Indeed, mice that are deficient in TGF-β (TGF-$\beta 1^{-/-}$)[103] survive for only a few weeks and die from lymphoproliferative disease. Furthermore, in the TNBS model, nasal instillation of a plasmid encoding TGF-β prevents colitis and also reverses established disease[104]. A potential problem with administering TGF-β is the pleiotropic nature of this cytokine, which can induce the activation of stromal cells leading to inflammation. Transfer of regulatory T-cell populations offers the advantage of delivering TGF-β locally, circumventing unwanted systemic effects. The study of regulatory T cells has converged recently with the finding that cells capable of inhibiting a range of autoimmune diseases, including diabetes, gastritis and inflammatory bowel disease, are contained within the $CD4^+$ $CD25^+$ subset. Inhibition of colitis by these cells is dependent on TGF-β. Importantly, this regulatory population constitutively expresses CTLA-4, which on binding can lead to the production of TGF-β. These regulatory cells have also been described in humans. The current view is that $CD25^+$ T cells originate in the thymus, perhaps as a distinct lineage, but it remains to be seen whether they are reduced or impaired in autoimmune conditions such as inflammatory bowel disease.

Bacterial flora

The incidence of colitis is significantly reduced in mice maintained under germ-free conditions, indicating that inflammation in the intestine is driven by resident bacteria.

This has been shown in a number of models, including the IL-10$^{-/-}$[105], IL-2$^{-/-}$[106] and the SCID models of colitis. It is also known that antibiotics can reduce the severity of colitis[107]. Nevertheless, not all bacteria are harmful; for example, repopulation of the colon of IL-10$^{-/-}$ mice with lactobacillus species prevents colitis[108]. There have been promising results using bacteria in ulcerative colitis. One study compared patients who, after standard treatment, were then maintained on mesalazine or a non-pathogenic strain of *Escherichia coli*[109]. Both maintenance treatments gave similar results.

Similarly, patients with chronic pouchitis who are maintained on a mixture of lactobacillus, bifidobacteria and *Streptococcus salivarius* (VSL#3) have remission rates that are significantly higher than those of patients receiving placebo[110]. These beneficial bacteria have come to be known an probiotics, but the mechanisms by which they act are unclear. Possible mechanisms include the production of antimicrobial products, the reduction of pH and reduced adherence of pathogenic bacteria. A novel approach is to use enteric bacteria as a vehicle for regulatory cytokines. This has been done by using the non-pathogenic murine bacteria *Lactococcus lactis* to secrete active IL-10[111], which ameliorated the spontaneous colitis in IL-10$^{-/-}$ mice that were fed the genetically modified bacteria. Probiotics have potential and are likely to enter standard clinical practice.

Conclusion

Animal models of colitis have contributed significantly to our understanding of inflammatory bowel disease. Their continued use will lead to further new treatment strategies. These strategies will be aimed at inhibiting inflammatory cytokines, at the transcription, secretion and receptor levels. Another approach is to utilize the natural regulatory mechanisms, including anti-inflammatory cytokines and cellular therapy with regulatory T cells. It is not yet clear how such new therapies will affect the surgical management of patients with inflammatory bowel disease or the overall outcome of treatment. It does seem likely, however, that they will soon have a profound impact.

Acknowledgements

The authors thank the Medical Research Council and the Royal College of Surgeons of England for funding this work. F. Powrie is funded by the Wellcome Trust.

References

1 Blumberg RS, Saubermann LJ, Strober W. Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. *Curr Opin Immunol* 1999; **11:** 648–56.

2 Wirtz S, Neurath MF. Animal models of intestinal inflammation: new insights into the molecular pathogenesis and immunotherapy of inflammatory bowel disease. *Int J Colorectal Dis* 2000; **15:** 144–60.

3 Sands BE. Therapy of inflammatory bowel disease. *Gastroenterology* 2000; **118**(Suppl 1): S68–82

4 O'Garra A. Cytokines induce the development of functionally heterogeneous T helper cell subsets. *Immunity* 1998, **8:** 275–83.

5 Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986, **136:** 2348–57.

6 Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE *et al.* A CD4$^+$ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; **389:** 737–42.

7 Asseman C, Powrie F. Interleukin 10 is a growth factor for a population of regulatory T cells. *Gut* 1998; **42:** 157–8.

8 Chen Y, Kuchroo VK, Inobe J, Hafler DA, Weiner HL. Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* 1994; **265:** 1237–40.

9 Seder RA, Paul WE. Acquisition of lymphokine-producing phenotype by CD4$^+$ T cells *Annu Rev Immunol* 1994; **12:** 635–73.

10 Szabo SJ, Dighe AS, Gubler U, Murphy KM. Regulation of the interleukin (IL)-12R beta 2 subunit expression in developing T helper 1 (Th1) and Th2 cells *J Exp Med* 1997; **185:** 817–24.

11 Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998; **115:** 182–205.

12 Pallone F, Monteleone G. Interleukin 12 and Th1 responses in inflammatory bowel disease. *Gut* 1998, **43:** 735–6.

13 Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D *et al.* A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. *J Immunol* 1997; **159:** 6276–82.

14 Monteleone G, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F *et al.* Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology* 1997; **112:** 1169–78.

15 Braegger CP, Nicholls S, Murch SH, Stephens S, MacDonald TT. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. *Lancet* 1992; **339:** 89–91.

16 Parrello T, Monteleone G, Cucchiara S, Monteleone I, Sebkova L, Doldo P *et al.* Up-regulation of the IL-12 receptor beta2 chain in Crohn's disease. *J Immunol* 2000; **165:** 7234–9.

17 Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA *et al* Disparate CD4$^+$ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996; **157:** 1261–70.

18 Parronchi P, Romagnani P, Annunziato F, Sampognaro S, Becchio A, Giannarini L *et al.* Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease. *Am J Pathol* 1997; **150:** 823–32.

19 Monteleone G, Trapasso F, Parrello T, Biancone L, Stella A, Iuliano R *et al.* Bioactive IL-18 expression is up-regulated in Crohn's disease. *J Immunol* 1999; **163:** 143–7.

20 Pizarro TT, Michie MH, Bentz M, Woraratanadharm J, Smith MF, Foley E *et al.* IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells. *J Immunol* 1999; **162:** 6829–35.

21 Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. *Annu Rev Med* 2000; **51:** 289–98.

22 Elson CO, Sartor RB, Tennyson GS, Riddell RH. Experimental models of inflammatory bowel disease. *Gastroenterology* 1995; **109:** 1344–67.

23 Madara JL, Podolsky DK, King NW, Sehgal PK, Moore R, Winter HS. Characterization of spontaneous colitis in cotton-top tamarins (*Saguinus oedipus*) and its response to sulfasalazine. *Gastroenterology* 1985; **88:** 13–19.

24 Sundberg JP, Elson CO, Bedigian H, Birkenmeier EH. Spontaneous heritable colitis in a new substrain of C3H/HeJ mice. *Gastroenterology* 1994; **107:** 1726–35.

25 Matsumoto S, Okabe Y, Setoyama H, Takayama K, Ohtsuka J, Funahashi H *et al.* Inflammatory bowel disease-like enteritis and caecitis in a senescence accelerated mouse P1/Yit strain. *Gut* 1998; **43:** 71–8.

26 Cong Y, Brandwein SL, McCabe RP, Lazenby A, Birkenmeier EH, Sundberg JP *et al.* CD4$^+$ T cells reactive to enteric bacterial antigens in spontaneously colitic C3H/HeJBir mice: increased T helper cell type 1 response and ability to transfer disease. *J Exp Med* 1998; **187:** 855–64.

27 Morris GP, Beck PL, Herridge MS, Depew WT, Szewczuk MR, Wallace JL. Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology* 1989; **96:** 795–803.

28 Elson CO, Beagley KW, Sharmanov AT, Fujihashi K, Kiyono H, Tennyson GS *et al.* Hapten-induced model of murine inflammatory bowel disease: mucosa immune responses and protection by tolerance. *J Immunol* 1996; **157:** 2174–85.

29 Boirivant M, Fuss IJ, Chu A, Strober W. Oxazolone colitis: a murine model of T helper cell type 2 colitis treatable with antibodies to interleukin 4. *J Exp Med* 1998; **188:** 1929–39.

30 Yamada T, Sartor RB, Marshall S, Specian RD, Grisham MB. Mucosal injury and inflammation in a model of chronic granulomatous colitis in rats. *Gastroenterology* 1993; **104:** 759–71.

31 Powrie F, Leach MW. Genetic and spontaneous models of inflammatory bowel disease in rodents: evidence for abnormalities in mucosal immune regulation. *Ther Immunol* 1995; **2:** 115–23.

32 Arbeit JM, Hirose R. Murine mentors: transgenic and knockout models of surgical disease. *Ann Surg* 1999; **229:** 21–40.

33 Hermiston ML, Gordon JI. Inflammatory bowel disease and adenomas in mice expressing a dominant negative N-cadherin. *Science* 1995; **270:** 1203–7.

34 Mashimo H, Wu DC, Podolsky DK, Fishman MC. Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor. *Science* 1996; **274:** 262–5.

35 Duchmann R, Schmitt E, Knolle P, Meyer zum Buschenfelde KH, Neurath M. Tolerance towards resident intestinal flora in mice is abrogated in experimental colitis and restored by treatment with interleukin-10 or antibodies to interleukin-12. *Eur J Immunol* 1996; **26:** 934–8.

36 Rennick DM, Fort MM. Lessons from genetically engineered animal models. XII. IL-10-deficient (IL-10$^{-/-}$) mice and intestinal inflammation. *Am J Physiol Gastrointest Liver Physiol* 2000; **278:** G829–33.

37 Ehrhardt RO, Ludviksson BR, Gray B, Neurath M, Strober W. Induction and prevention of colonic inflammation in IL-2-deficient mice. *J Immunol* 1997; **158:** 566–73.

38 Spencer SD, Di Marco F, Hooley J, Pitts-Meek S, Bauer M, Ryan AM *et al.* The orphan receptor CRF2-4 is an essential subunit of the interleukin 10 receptor. *J Exp Med* 1998; **187:** 571–8.

39 Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity* 1999; **10:** 387–98.

40 Kollias G, Douni E, Kassiotis G, Kontoyiannis D. On the role of tumor necrosis factor and receptors in models of multiorgan failure, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. *Immunol Rev* 1999; **169:** 175–94.

41 Bhan AK, Mizoguchi E, Smith RN, Mizoguchi A. Colitis in transgenic and knockout animals as models of human inflammatory bowel disease. *Immunol Rev* 1999; **169:** 195–207.

42 Iijima H, Takahashi I, Kishi D, Kim JK, Kawano S, Hori M *et al.* Alteration of interleukin 4 production results in the inhibition of T helper type 2 cell-dominated inflammatory bowel disease in T cell receptor alpha chain-deficient mice. *J Exp Med* 1999; **190:** 607–15.

43 Mizoguchi A, Mizoguchi E, Bhan AK. The critical role of interleukin 4 but not interferon gamma in the pathogenesis of colitis in T-cell receptor alpha mutant mice. *Gastroenterology* 1999; **116:** 320–6.

44 Mizoguchi A, Mizoguchi E, Chiba C, Bhan AK. Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice. *J Exp Med* 1996; **184:** 707–15.

45 Powrie F, Leach MW, Mauze S, Caddle LB, Coffman RL. Phenotypically distinct subsets of CD4$^+$ T cells induce or protect from chronic intestinal inflammation in C.B-17 SCID mice. *Int Immunol* 1993; **5:** 1461–71.

46 De Winter H, Cheroutre H, Kronenberg M. Mucosal immunity and inflammation. II. The yin and yang of T cells in intestinal inflammation: pathogenic and protective roles in a mouse colitis model. *Am J Physiol* 1999; **276:** G1317–21.

47 Leach MW, Bean AG, Mauze S, Coffman RL, Powrie F. Inflammatory bowel disease in C.B-17 SCID mice reconstituted with the CD45RB^{high} subset of CD4$^+$ T cells. *Am J Pathol* 1996; **148:** 1503–15.

48 Powrie F. T cells in inflammatory bowel disease: protective and pathogenic roles. *Immunity* 1995; **3:** 171–4.

49 Read S, Malmstrom V, Powrie F. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+) CD4(+) regulatory cells that control intestinal inflammation. *J Exp Med* 2000; **192:** 295–302.

50 Sakaguchi S. Regulatory T cells: key controllers of immunologic self-tolerance. *Cell* 2000; **101:** 455–8.

51 Shevach EM. Regulatory T cells in autoimmmunity. *Annu Rev Immunol* 2000; **18:** 423–49.

52 Duchmann R, May E, Heike M, Knolle P, Neurath M, Meyer zum Buschenfelde KH. T cell specificity and cross reactivity towards enterobacteria, bacteroides, bifidobacterium, and antigens from resident intestinal flora in humans. *Gut* 1999; **44:** 812–18.

53 Powrie F, Leach MW, Mauze S, Menon S, Caddle LB, Coffman RL. Inhibition of Th1 responses prevents inflammatory bowel disease in SCID mice reconstituted with CD45RB^{hi} CD4$^+$ T cells. *Immunity* 1994; **1:** 553–62.

54 Baert FJ, Rutgeerts PR. Anti-TNF strategies in Crohn's disease: mechanisms, clinical effects, indications. *Int J Colorectal Dis* 1999; **14:** 47–51.

55 Bell S, Kamm MA. Antibodies to tumour necrosis factor alpha as treatment for Crohn's disease. *Lancet* 2000; **355:** 858–60.

56 van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, Jansen J, Tytgat GN *et al.* Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 1995; **109:** 129–35.

57 Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337:** 1029–35.

58 D'Haens G, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F *et al.* Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 1999; **116:** 1029–34.

59 Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D *et al.* Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999; **116:** 22–8.

60 Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH *et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117:** 761–9.

61 Vasiliauskas EA, Kam LY, Karp LC, Gaiennie J, Yang H, Targan SR. Marker antibody expression stratifies Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics. *Gut* 2000; **47:** 487–96.

62 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340:** 1398–405.

63 Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Successful management of Crohn's disease of the ileoanal pouch with infliximab. *Gastroenterology* 1999; **117:** 429–32.

64 Stack WA, Mann SD, Roy AJ. Heath P, Sopwith M, Freeman J *et al.* Randomised controlled trial of CDP571 antibody to tumour necrosis factor-alpha in Crohn's disease. *Lancet* 1997; **349:** 521–4.

65 Bickston SJ, Lichtenstein GR, Arseneau KO, Cohen RB, Cominelli F. The relationship between infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999; **117:** 1433–7.

66 Greenstein AJ, Mullin GE, Strauchen JA, Heimann T, Janowitz HD, Aufses AH Jr *et al.* Lymphoma in inflammatory bowel disease. *Cancer* 1992; **69:** 1119–23.

67 Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL *et al.* Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997; **337:** 141–7.

68 Ehrenpreis ED, Kane SV, Cohen LB, Cohen RD, Hanauer SB. Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117:** 1271–7.

69 Vasiliauskas EA, Kam LY, Abreu-Martin MT, Hassard PV, Papadakis KA, Yang H *et al.* An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117:** 1278–87.

70 Leach MW, Davidson NJ, Fort MM, Powrie F, Rennick DM. The role of IL-10 in inflammatory bowel disease: 'of mice and men'. *Toxicol Pathol* 1999; **27:** 123–33.

71 Pender SL, Breese EJ, Gunther U, Howie D, Wathen NC, Schuppan D *et al.* Suppression of T cell-mediated injury in human gut by interleukin 10: role of matrix metalloproteinases. *Gastroenterology* 1998; **115:** 573–83.

72 Hagenbaugh A, Sharma S, Dubinett SM, Wei SHY, Aranda R, Cheroutre H *et al.* Altered immune responses in interleukin 10 transgenic mice. *J Exp Med* 1997; **185:** 2101–10.

73 Asseman C, Mauze S, Leach MW, Coffman RL, Powrie F. An essential role for interleukin 10 in the function of regulatory T cells that inhibit intestinal inflammation. *J Exp Med* 1999; **190:** 995–1004.

74 Barbara G, Xing Z, Hogaboam CM, Gauldie J, Collins SM. Interleukin 10 gene transfer prevents experimental colitis in rats. *Gut* 2000; **46:** 344–9.

75 Herfarth HH, Mohanty SP, Rath HC, Tonkonogy S, Sartor RB. Interleukin 10 suppresses experimental chronic, granulomatous inflammation induced by bacterial cell wall polymers. *Gut* 1996; **39:** 836–45.

76 Fedorak RN, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G *et al.* Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's

disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology* 2000; **119:** 1473–82.

77 Schreiber S, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S *et al.* Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. *Gastroenterology* 2000; **119:** 1461–72.

78 van Deventer SJ, Elson CO, Fedorak RN. Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group. *Gastroenterology* 1997; **113:** 383–9.

79 Greenwood-Van Meerveld B, Tyler K, Keith JC Jr. Recombinant human interleukin-11 modulates ion transport and mucosal inflammation in the small intestine and colon. *Lab Invest* 2000; **80:** 1269–80.

80 Sands BE, Bank S, Sninsky CA, Robinson M, Katz S, Singleton JW *et al.* Preliminary evaluation of safety and activity of recombinant human interleukin 11 in patients with active Crohn's disease. *Gastroenterology* 1999; **117:** 58–64.

81 Sans M, Panes J, Ardite E, Elizalde JI, Arce Y, Elena M *et al.* VCAM-1 and ICAM-1 mediate leukocyte–endothelial cell adhesion in rat experimental colitis. *Gastroenterology* 1999; **116:** 874–83.

82 Hesterberg PE, Winsor-Hines D, Briskin MJ, Soler-Ferran D, Merrill C, Mackay CR *et al.* Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin alpha 4 beta 7. *Gastroenterology* 1996; **111:** 1373–80.

83 Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL *et al.* A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. *Gastroenterology* 1998; **114:** 1133–42.

84 Battaglia E, Biancone L, Resegotti A, Emanuelli G, Fronda GR, Camussi G. Expression of CD40 and its ligand, CD40L, in intestinal lesions of Crohn's disease. *Am J Gastroenterol* 1999; **94:** 3279–84.

85 Liu Z, Colpaert S, D'Haens GR, Kasran A, de Boer M, Rutgeerts P *et al.* Hyperexpression of CD40 ligand (CD154) in inflammatory bowel disease and its contribution to pathogenic cytokine production. *J Immunol* 1999; **163:** 4049–57.

86 Stuber E, Strober W, Neurath M. Blocking the CD40L–CD40 interaction *in vivo* specifically prevents the priming of T helper 1 cells through the inhibition of interleukin 12 secretion. *J Exp Med* 1996; **183:** 693–8.

87 Liu Z, Geboes K, Colpaert S, Overbergh L, Mathieu C, Heremans H *et al.* Prevention of experimental colitis in SCID mice reconstituted with CD45RB^{high} CD4$^+$ T cells by blocking the CD40–CD154 interactions. *J Immunol* 2000; **164:** 6005–14.

88 De Jong YP, Comiskey M, Kalled SL, Mizoguchi E, Flavell RA, Bhan AK *et al.* Chronic murine colitis is dependent on the CD154/CD40 pathway and can be attenuated by anti-CD154 administration. *Gastroenterology* 2000; **119:** 715–23.

89 Kirk AD, Burkly LC, Batty DS, Baumgartner RE, Berning JD, Buchanan K *et al.* Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. *Nature Med* 1999; **5:** 686–93.

90 Wirtz S, Finotto S, Kanzler S, Lohse AW, Blessing M, Lehr HA *et al.* Cutting edge: chronic intestinal inflammation in STAT-4 transgenic mice: characterization of disease and adoptive transfer by TNF- plus IFN-gamma-producing CD4$^+$ T cells that respond to bacterial antigens. *J Immunol* 1999; **162:** 1884–8.

91 Simpson SJ, Shah S, Comiskey M, de Jong YP, Wang B, Mizoguchi E *et al.* T cell-mediated pathology in two models of experimental colitis depends predominantly on the interleukin 12/signal transducer and activator of transcription (Stat)-4 pathway, but is not conditional on interferon gamma expression by T cells. *J Exp Med* 1998; **187:** 1225–34.

92 Monteleone G, MacDonald TT, Wathen NC, Pallone F, Pender SL. Enhancing lamina propria Th1 cell responses with interleukin 12 produces severe tissue injury. *Gastroenterology* 1999; **117:** 1069–77.

93 Neurath MF, Fuss I, Kelsall BL, Stuber E, Strober W. Antibodies to interleukin 12 abrogate established experimental colitis in mice. *J Exp Med* 1995; **182:** 1281–90.

94 Fuss IJ, Marth T, Neurath MF, Pearlstein GR, Jain A, Strober W. Anti-interleukin 12 treatment regulates apoptosis of Th1 T cells in experimental colitis in mice. *Gastroenterology* 1999; **117:** 1078–88.

95 Davidson NJ, Hudak SA, Lesley RE, Menon S, Leach MW, Rennick DM. IL-12, but not IFN-gamma, plays a major role in sustaining the chronic phase of colitis in IL-10-deficient mice. *J Immunol* 1998; **161:** 3143–9.

96 Sakai T, Kusugami K, Nishimura H, Ando T, Yamaguchi T, Ohsuga M *et al.* Interleukin 15 activity in the rectal mucosa of inflammatory bowel disease. *Gastroenterology* 1998; **114:** 1237–43.

97 Monteleone G, Parrello T, Luzza F, Pallone F. Response of human intestinal lamina propria T lymphocytes to interleukin 12: additive effects of interleukin 15 and 7. *Gut* 1998; **43:** 620–8.

98 Watanabe M, Ueno Y, Yajima T, Okamoto S, Hayashi T, Yamazaki M *et al.* Interleukin 7 transgenic mice develop chronic colitis with decreased interleukin 7 protein accumulation in the colonic mucosa. *J Exp Med* 1998; **187:** 389–402.

99 Atreya R, Mudter J, Finotto S, Mullberg J, Jostock T, Wirtz S *et al.* Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis *in vivo*. *Nature Med* 2000; **6:** 583–8.

100 Yamamoto M, Yoshizaki K, Kishimoto T, Ito H. IL-6 is required for the development of Th1 cell-mediated murine colitis. *J Immunol* 2000; **164:** 4878–82.

101 Keates AC, Castagliuolo I, Cruickshank WW, Qiu B, Arseneau KO, Brazer W *et al.* Interleukin 16 is up-regulated in Crohn's disease and participates in TNBS colitis in mice. *Gastroenterology* 2000; **119:** 972–82.

102 Powrie F, Carlino J, Leach MW, Mauze S, Coffman RL. A critical role for transforming growth factor-beta but not interleukin 4 in the suppression of T helper type 1-mediated colitis by CD45RB (low) CD4$^+$ T cells. *J Exp Med* 1996; **183:** 2669–74.

103 Shull MM, Ormsby I, Kier AB, Pawlowski S, Diebold RJ, Yin M *et al.* Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. *Nature* 1992; **359:** 693–9.

104 Kitani A, Fuss IJ, Nakamura K, Schwartz OM, Usui T, Strober W. Treatment of experimental (trinitrobenzene sulfonic acid) colitis by intranasal administration of transforming growth factor (TGF)-beta1 plasmid: TGF-beta1-mediated suppression of T helper cell type 1 response occurs by interleukin (IL)-10 induction and IL-12 receptor beta2 chain downregulation. *J Exp Med* 2000; **192:** 41–52.

105 Sellon RK, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E *et al.* Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun* 1998; **66:** 5224–31.

106 Schultz M, Tonkonogy SL, Sellon RK, Veltkamp C, Godfrey VL, Kwon J *et al.* IL-2-deficient mice raised under germfree conditions develop delayed mild focal intestinal inflammation. *Am J Physiol* 1999; **276:** G1461–72.

107 Madsen KL, Doyle JS, Tavernini MM, Jewell LD, Rennie RP, Fedorak RN. Antibiotic therapy attenuates colitis in interleukin 10 gene-deficient mice. *Gastroenterology* 2000; **118:** 1094–105.

108 Madsen KL, Doyle JS, Jewell LD, Tavernini MM, Fedorak RN. Lactobacillus species prevents colitis in interleukin 10 gene-deficient mice. *Gastroenterology* 1999; **116:** 1107–14.

109 Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli versus* mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999; **354:** 635–9.

110 Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G *et al.* Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119:** 305–9.

111 Steidler L, Hans W, Schotte L, Neirynck S, Obermeier F, Falk W *et al.* Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. *Science* 2000; **289:** 1352–5.

Calcutta University College of Medicine
LIBRARY
C. U.

Review

Suspected acute appendicitis: trends in management over 30 years

P. F. Jones

Department of Surgery, University of Aberdeen, Aberdeen, UK
Correspondence to: Professor P. F. Jones, 7 Park Road, Cults, Aberdeen AB15 9HR, UK

Background: Tradition taught that patients with signs suspicious of acute appendicitis should be explored surgically, but studies in the 1960s found that if this group was closely observed about one-third recovered without treatment. To differentiate these patients a strict regimen of active observation was introduced and this has now been studied over 30 years. Ultrasonography, laparoscopy and computed tomography (CT) have also been used to clarify the diagnosis in these patients.

Methods: Papers on the management of patients with suspected appendicitis published since 1970 were traced through Index Medicus, English-language journals and Medline. All those that mention the use of observation are reviewed, with selective reports on the other methods used. The advantages and disadvantages of various methods of management are compared.

Results and conclusion: Active observation has yielded a consistently low negative appendicectomy rate without a rise in the perforation rate; there was one death in over 1600 patients. It has proved to be a practical method of discriminating between patients who do and do not need an operation. In this situation, both ultrasonography and CT yield some false-negative reports, so results must be checked at the bedside. Furthermore, CT involves exposure to significant doses of radiation.

Paper accepted 2 July 2001

British Journal of Surgery 2001, **88**, 1570–1577

Introduction

Although more than 100 years have passed since Reginald Fitz, Professor of Pathology at Harvard University, coined the term 'appendicitis' and went on to stress 'the vital importance of early recognition of perforated appendicitis'[1], the best management of patients believed to have acute appendicitis is still the subject of keen debate. In 1900 Riddell[2] in Aberdeen reported that 'no case of acute perforative appendicitis if left to nature recovers, but with operation the patient has a chance'. In the London Hospital in 1905 the overall mortality rate was 26 per cent, while in 166 patients who had developed general peritonitis the mortality rate was 76 per cent[3]. With this experience of the dangers of perforation it is understandable that, in a doubtful case, surgeons felt obliged to operate without delay. As experience grew, and there were advances in the management of peritonitis and techniques of resuscitation and anaesthesia, mortality rates fell by 1948 to about 1 per cent[4]. By then, however, this policy of precautionary appendicectomy had become a tradition and surgeons in training believed their experienced teachers when they advised that 'delaying appendectomy to achieve greater diagnostic accuracy ... must cause more perforations'[5]. When in doubt the trainee was clearly expected to operate.

Although the overall mortality rate associated with acute appendicitis has now fallen to about one in 600[6], this tradition has prevailed in many centres, which report negative appendicectomy rates of 20–30 per cent[7]. For many years ways have been sought to reduce this figure by achieving a better discrimination between patients who do and who do not need surgical exploration. Scoring systems and computer-assisted diagnosis have proved useful, largely because any stimulus towards the accurate elicitation and analysis of symptoms and signs raises interest in differential diagnosis[8]. Ultrasonography has now had an extended trial and can often yield valuable information in the hands of a skilled sonographer. In recent years, especially in North America, computed tomography (CT) has been shown to yield precise information and is now being used to screen al doubtful cases. Still, there must be doubts about thi development, which exposes children and young adults to significant dose of radiation[9]. Before accepting this application it is right to ask whether there are simpler ways of achieving good diagnostic discrimination.

Epidemiology of acute abdominal pain

In the 1960s several audits were conducted on all patients coming to hospital complaining of acute abdominal pain of less than 1 week's duration. Among 785 children seen consecutively over 3 years, of whom over 90 per cent were referred with suspected appendicitis, it was surprising to find that as many as one-third had steadily improved after admission, without treatment, and returned home within 24–48 h[10]. For the surgeons of the hospital this finding was not unexpected (although its frequency was) because at that time they were quite often asked by family doctors to undertake domiciliary consultations. From time to time a surgeon would see a child at home who presented a generally convincing picture of early acute appendicitis and admission was arranged. On examining the child a few hours later in the ward, with the operating theatre prepared, the symptoms and signs were found to have eased, operation was postponed and a full recovery followed. After a few of these experiences it was possible to understand why such children had been referred to hospital and how, after a single examination, could have been candidates for precautionary appendicectomy. Their symptoms and signs were compared with those in children who had acute appendicitis and, although when first seen almost all had pain and tenderness in the right lower quadrant, over a few hours clear differences became apparent.

In Aberdeen some 300 children proved to have this self-limiting condition and it was named 'acute non-specific abdominal pain'[10]. It was necessary to ensure that there was not among this group a number of children who soon needed readmission. Some 325 records were checked between 6 months and 2 years after discharge of such children and only 18 had required readmission, six with acute appendicitis, three with other surgical conditions such as intussusception and nine with another self-limiting attack of pain[10]. Confirmation of the existence of acute non-specific abdominal pain was provided in 1970 by the Oxford Record Linkage Study, which found that during 1962–1963 'abdominal pain for which no definite explanation could be found' was the sixth most common cause of admission to Oxford hospitals among females, and the tenth most common among men[11].

At this time de Dombal in Leeds was beginning his studies of computer-assisted diagnosis of 'acute abdominal pain which had arisen within 1 week of admission', and from the start it was clear that in Leeds adult patients with non-specific pain were at least as numerous as those with appendicitis[12]. In the years that followed de Dombal extended his studies to other UK hospitals, and then to countries as widely separated as the USA, South Africa, Norway, Thailand and Australia. Figures for admissions for acute abdominal pain collected in 26 centres, in 17 countries, and in 10 320 patients showed the three commonest categories to be non-specific pain (34 per cent), acute appendicitis (28 per cent) and acute cholecystitis (10 per cent). In spite of the wide geographical spread of the centres there was a marked similarity in the clinical picture that they presented[13].

The condition of acute non-specific abdominal pain has been studied carefully and, although its origins remain unclear and are probably multifactorial, there is no doubt about its frequent occurrence[14]. This must affect management because, if one-third of patients with suspected appendicitis eventually recovers without treatment, it is not wise to pursue a policy of deciding on diagnosis and management immediately the patient arrives in hospital. Some clearly need an operation urgently but, if time is not allowed for those who may have non-specific pain to declare themselves, many negative appendicectomies will result. In the early 1970s the only way of differentiating these patients was to maintain close observation on all patients with equivocal signs.

Active observation

In view of the widespread belief that observation of the undiagnosed patient carried a serious risk of perforation of the appendix, in the 1970s a study was carried out in which each patient was assigned to a diligent structured regimen which was called active observation[15]. Intravenous fluids were administered and oral intake was forbidden, sedation was given as necessary, regular nursing recordings and observations were made, and urine and blood tests were performed. Serial estimations of the white cell count (and more recently of C-reactive protein) were made when indicated. After 2–3 h the surgeon (preferably the same individual) reassessed the situation and at this stage this large group (about two-thirds of all the patients) separated into three categories:

1. In a number of patients (especially children) a medical cause for the pain was confirmed, e.g. an acute respiratory or urinary tract infection, a major degree of constipation, or a rarity such as diabetic ketoacidosis. Appropriate treatment was started.
2. A small, but important, group after a few hours showed more convincing signs of intraperitoneal pathology. In children and in men this usually meant that an operation for surgical pathology was required. Among females the situation was more complex. Pregnancy testing was often

required and the implications of a positive result considered. Pelvic inflammatory disease and ovarian abnormalities that did not need operation were common; expert assessment was often needed and laparoscopy may be helpful in this situation[16].

3 In the remaining group (30–40 per cent of all patients) a firm diagnosis was not possible at this first re-examination, although the majority showed signs of improvement. After a further period of active observation it was clear that most had recovered and could, in retrospect, be considered to have experienced an episode of acute non-specific abdominal pain.

In a minority of patients symptoms and signs persist and the diagnosis remains uncertain. Experience has shown that they can safely remain under active observation, with such tests as are needed being performed, including repetition of the white cell count and measurement of C-reactive protein. Ultrasonography may be useful. Some will require surgical exploration which, apart from acute appendicitis, may reveal Meckel's diverticulitis, sigmoid or caecal diverticulitis, the occasional carcinoid of the appendix or ovarian abnormalities[16]. The wish of the surgeon to avoid an unproductive operation must not at this point inhibit the decision to operate. Surgeons who practise active observation learn that there are occasions when signs persist and the only safe course is to explore. Sometimes the result is negative but there is no discredit in this when every care has been taken before taking the decision to operate, but there are also occasions when a black distended appendix has needed to be gently removed as it lay just over the pelvic brim or behind the ileum, where it was protected from direct pressure from the abdomen or at rectal examination.

Risk of perforation

This risk has lain behind many early and unproductive explorations, but the trials of active observation have shown that the time taken is not followed by a rise in the perforation rate. *Table 1* summarizes the results of these trials which cover more than 25 years and over 1600 patients. The negative appendicectomy rate is low, and there was one death in a child admitted with advanced peritonitis. Perforation rates are quoted in four reports[15,17,19,20] in which 402 acutely inflamed appendices were removed, of which 87 (22 per cent) were perforated. Of these, 80 were removed promptly on admission, two patients required resuscitation before operation and only five came to operation after observation, with a good recovery in every case. This experience is confirmed in other reports. Walker *et al.*[28] found in 248 patients of all ages that a delay of up to 24 h before operation did not significantly affect either the perforation rate or the length of stay in

Table 1 Negative appendicectomy rates among patients with suspected acute appendicitis

Reference	Year	Centre	Children or adults	Total no. of patients	No. with proven appendicitis	No. with other surgical emergency	No. of normal appendices removed
Active observation*							
White *et al.*[17]	1975	Baltimore	C	104	98	2	4 (4)
White *et al.*[17]	1975	Baltimore	A	74	67	4	3 (4)
Jones[15]	1976	Aberdeen	C	119	102	5	12 (10)
O'Donnell[18]	1985	Dublin	C	500	455	0	45 (9)
Thomson and Jones[19]	1986	Inverness	C + A	48	42	2	4 (8)
Dolgin *et al.*[20]	1992	New York	C	100	93	1	6 (6)
Driver and Youngson[21]	1995	Aberdeen	C	87	78	6	3 (3)
Senbanjo[22]	1997	Saudi Arabia	C + A	135	113	10	12 (9)
Bachoo *et al.*[23]	2001	Aberdeen	C	451	439	0	12 (3)
Colson *et al.*[24]†	1997	Los Angeles	A	659	599	19	41 (6)
Bergeron *et al.*[25]†	1999	Quebec	C + A	214	196	0	18 (8)
Total				2491			160 (6)
Observation not used							
Jones[10]	1969	Aberdeen	C	462	398	0	64 (14)
White *et al.*[17]	1975	Baltimore	C	266	213	4	49 (18)
O'Donnell[18]	1985	Dublin	C	3677	2694	0	983 (27)
Lewis *et al.*[26]	1975	San Francisco	C + A	972	772	0	200 (21)
Andersson *et al.*[27]	1992	Jönköping	C + A	3029	2100	105	824 (27)
Walker *et al.*[28]	1995	Liverpool	C + A	248	182	3	63 (25)
Rao *et al.*[9]	1999	Boston	C + A	493	395	0	98 (20)

Values in parentheses are percentages. *One recorded death in these reports. †Not stated whether trial of active observation, but use of observation mentioned specifically. C, children; A, adults hospital. McLean *et al.*[29] operated on 578 patients with suspected appendicitis. As the time between admission and operation increased the proportion of unnecessary operations actually fell, with no increase in the incidence of gangrene or perforation of the appendices removed. However, among operations performed within 2 h of admission as many as 39 per cent were considered to be unnecessary and the authors advised that 'unless diagnosis is clear the patient should be placed under active clinical review'. Surana *et al.*[30] decided to avoid operating for acute appendicitis between midnight and 08.00 hours. They compared the results in 244 children whose operation was postponed for 6–18 h with those of 451 operated on within 6 h of admission; there was no statistically significant difference in perforation rates (21 and 18 per cent respectively), complications or length of hospital stay, and there were no deaths.

Jackson[31] found that there were two elements causing delay in admission to hospital, one related to parents of affected children who were slow to call the family doctor and the other related to the doctor returning to the home for reassessment before deciding to send the child to hospital. He concluded that rupture of the appendix is 'related almost entirely to the duration of illness before admission'. By the time of admission signs may be very marked and Jackson found that among 140 children with a perforated appendix only in four was there any hesitation before the decision to operate. In Edinburgh, UK, a prospective study found that among 275 patients with proven acute appendicitis, 78 had a gangrenous or perforated organ, and a mean of 41 h had elapsed before their admission; this compared with a mean 18-h delay among 197 patients with phlegmonous appendicitis[32]. Another prospective study in Calgary, Canada, collected similar figures; the length of time that elapsed before admission in the two groups was respectively 51 and 22 h[33]. In Boston also it was noted in one series that all the children with a perforated appendix were clearly in need of operation at the time of admission to hospital[17]. It must also be remembered that, although the perforation rate in infancy is about 50 per cent, it falls steadily thereafter and between 10 and 40 years of age it is about 10 per cent; there is then a steady rise to about 30 per cent at 60 years of age, and beyond 75 years the rate returns to about 50 per cent[34]. At the ages when appendicitis is most often encountered, therefore, the risk of perforation is at its lowest, but special vigilance is needed at the extremes of age. When all these reports are gathered together they provide a substantial basis for the continued use of active observation as a safe and effective method of managing patients with suspected appendicitis.

Before leaving the subject of observation a cautionary note is needed. All those who use the method have a responsibility to remember that, although symptoms and signs quickly resolve in those with non-specific pain, this term is not a diagnosis. It characterizes a real and common syndrome but, because most patients leave hospital without extensive investigation, it is possible (particularly in older patients) for the symptoms to settle but still leave significant pathology unrecognized. De Dombal *et al.*[35] studied 5675 patients with acute abdominal pain presenting at five hospitals and found that among patients over 50 years old who left hospital after an episode of non-specific pain 11 per cent were suffering from cancer (half affecting the colon and rectum). The true cause of their pain became evident over the year following admission and so there is a sound case for screening patients with non-specific pain who are over 50 years of age in the weeks after they leave hospital. Few younger patients have persistent complaints, but the possibility should not be overlooked; occasionally a condition such as Crohn's disease is found.

Reducing the negative appendicectomy rate

Table 1 shows that active observation results in a substantial fall in the negative appendicectomy rate, and this coincides with a growing recognition of the disadvantages that these operations impose on patients and hospitals. The interruption to daily activities of patients can be serious and the waste of hospital resources is considerable. Troublesome complications follow some negative explorations, including wound sepsis, residual abscesses, respiratory and urinary tract infections, and late adhesive small bowel obstruction requiring laparotomy[36–38]. It must be difficult for patients to accept the upset of the operation, and the occasional setbacks, when they suspect that surgery might have been avoided. There is reason for concern where negative appendicectomy rates of 20–30 per cent continue to be quoted and, apart from active observation, there have been other developments directed at improving the quality of management of patients sent to hospital with suspected appendicitis. One involves the selective use of laparoscopy. Another, quite different, approach is to use ultrasonography or CT to distinguish those who require admission from those who do not.

Laparoscopy

Laparoscopy has been used increasingly since Sugarbaker *et al.*[39] demonstrated its potential in 1975, and Deutsch *et al.*[40] in 1982 laparoscoped 36 women between 18 and 45 years of age in whom 'appendicitis seemed the most likely diagnosis'. In 20 an acutely inflamed appendix was removed; however, nine had salpingitis and three a ruptured follicular cyst, and the operation was terminated. Since then there have been many reports on the value of diagnostic laparoscopy, largely in younger women, with similar results, and there is now enough information on which to base some conclusions.

Diagnostic laparoscopy is not often needed in children or in men with suspected appendicitis because when the signs, either on admission or after observation, show that operation is needed a surgical condition is nearly always found. When 100 men aged between 15 and 65 years were considered to need operation for acute appendicitis the diagnosis was confirmed histologically in 94[41], and *Table 1* shows the low negative appendicectomy rates recorded among children who were managed with active observation.

Among women of childbearing age, in whom gynaecological and obstetric causes of abdominal pain are common and which may not require surgical treatment, there is considerable scope for laparoscopy. If the signs do not show an immediate need for operation it is reasonable to institute active observation and carry out necessary investigations. A number of these patients will prove to have non-specific pain and can be discharged. Others will show persistent signs and laparoscopy is often appropriate. In Amsterdam 1050 consecutive patients were referred by their family doctors with suspected appendicitis, of whom 45 per cent proceeded to appendicectomy (13 per cent normal) and 19 per cent settled under observation[42]. It was decided to laparoscope the remaining 377 patients (36 per cent), of whom 67 per cent were women and 11 per cent children. In 268 the appendix was removed, 41 (15 per cent) proving to be normal. In 48 women a gynaecological source of pain was found, including ovulatory bleeding (13) and salpingitis (nine); four torsions of an ovarian cyst and three tubal pregnancies were removed.

There has been much debate over whether to remove an appendix which, at laparoscopy, looks normal. In the Amsterdam series, 100 of the 109 patients who did not have the appendix removed were followed; after a median time of 4·4 years only two had had acute appendicitis, with nine having had some recurrent pain. The conclusion was that the management policy had been reasonable and this notion is quite widely shared[42]. However, from the point of view of the patient, a visit to the operating theatre and general anaesthesia count as an operation, and consent will have been given for appendicectomy, if indicated. If on waking the patient learns that the appendix looked normal and was not removed, this must be made quite clear, because there will be a tendency over time to assume removal. Some patients will understandably regret that this was not done. From a pathological viewpoint there is a sound argument for removal and histological examination in every case. In one series of 175 operations for suspected appendicitis 43 normal-looking appendices were removed and the histology showed acute inflammation in 11[43]. Another report must also be remembered in which 40 carcinoids of the appendix were removed over 30 years from children living around Birmingham, UK[44]. All were identified at emergency operations for suspected appendicitis, and only four appendices had appeared to be abnormal to the surgeon. Leaving the normal-looking appendix in position lowers the negative appendicectomy rate, but this may not be in the best interest of the patient.

Recently it has been suggested that laparoscopy might be used as a screening procedure in those with suspected appendicitis who do not immediately need an operation. Of 120 such patients, 59 had a laparoscopy shortly after admission[45] and the diagnostic yield was greater than that among the 61 contemporary patients who were observed; two ovarian tumours and one caecal carcinoma were identified. This regimen also meant that among the 59 patients who were given a general anaesthetic and laparoscoped there were 11 patients who proved to have non-specific pain. Laparoscopy is not wholly free from risk and it is questionable whether it should be imposed on a group that is at no risk of appendicitis. It seems wiser to use active observation first, which should identify most patients with non-specific pain, and reserve laparoscopy for those who need it.

Ultrasonography and computed tomography

Ultrasonography has an established position as a valuable investigation in selected individuals. It is non-invasive, safe for use in children and during pregnancy, and able to make a particular contribution in gynaecological problems. Recently it has been used to scan all patients with suspected appendicitis, in the hope that it will differentiate those who need admission from those who can safely go home. While accuracy is over 93 per cent in the hands of experienced ultrasonographers, in a trial of 129 patients there was still a problem because 'false-negative reports do occur … and there is no certain way of determining which negative report is a false negative. Patients cannot be safely sent home after a negative result unless there are good clinical grounds for their discharge'[46]. In another trial of 152 consecutive patients, Davies *et al.*[47] found that 'the figures for ultrasound detection of acute appendicitis were no better than the clinical diagnosis of the admitting surgeon'.

This failure of ultrasonography to produce clear-cut results has led to a number of studies in North America of the ability of appendiceal CT to produce more precise information[48]. Some reports come from teaching hospitals where experienced radiologists produce accuracy rates in excess of 95 per cent, and where the claim is made that CT scanning of patients in the emergency room allows many with suspected appendicitis, who would otherwise incur the expense of admission, to be given the all-clear. In Boston 415 patients aged between 2 and 85 years were seen in the emergency room; 86 had an immediate appendicectomy and 329 (including 75 children) had helical contrast-enhanced CT of the appendix (with a mean of 900 ml Gastrografin solution (Bristol-Myers Squibb, Wallingford, Connecticut, USA) being run into the rectum)[9]. Appendicectomy for proven acute appendicitis was performed in 123 patients, there being delay in one patient who had a false-negative report. In 206 of the 329 patients no operation was performed; in 105 patients other conditions were identified, including ileocolitis (27), ovarian cyst (22), diverticular disease (six) and small bowel obstruction (five). The CT result in 101 patients was negative and it seems reasonable to infer that many of them would have proved to have non-specific pain under active observation, and would have been spared appreciable irradiation. The negative appendicectomy rate fell from 20 per cent before the use of CT to 7 per cent after its introduction[9]; with active observation the negative appendicectomy rate is 6 per cent (*Table 1*).

Other reports strike a more cautious note. In a prospective survey of 625 patients in New York who were operated on for suspected appendicitis over 5 years, surgeons requested helical contrast-enhanced CT for 261 patients (this involved giving combinations of oral and intravenous Gastrografin solutions). Although use of such CT rose from 25 per cent of eligible patients in the first year to 68 per cent in the fifth year, the negative appendicectomy rate remained largely unchanged, which suggests that the results of such imaging had a limited influence on decision making[49]. Among 107 patients in Dallas, Texas who were imaged there were three false-negative results, and the authors of the report concluded was that 'although helical contrast-enhanced CT has proven to be highly accurate, it is still only an adjunct to the diagnosis of appendicitis. A good clinical examination cannot be replaced'[50].

This reserved conclusion, which is very similar to the assessment of ultrasonography, is sufficient to raise questions over the wisdom of using an interventional and expensive investigation on so many people, of whom fewer than 40 per cent will prove to have acute appendicitis[9,51]. Even more compelling is the fact that CT involves the exposure of children, young people and possibly pregnant women to a significant dose of radiation. It is difficult to obtain definite figures, but it seems likely that helical CT for diagnosis of appendicitis produces a dose of about 3 mSv, which is four times the dose received in plain abdominal radiography and about 100 times the dose in postero-anterior chest radiography[52]. It must also be remembered that children often receive a dose that, in relative terms, exceeds the adult dose; more attention is now being paid to this aspect[53].

Conclusion

In the search for better methods of management of patients with suspected appendicitis, whose signs do not call for prompt operation, it is necessary for the response to be proportionate to the risks. Symptoms and signs resolve given time in about one-third of cases, and active observation offers a safe and effective method of identifying most of these patients. Protocols that require the administration of general anaesthesia or a significant dose of radiation to the whole group expose these patients to risks that are out of proportion to the problem to be solved. Schwartz[54] has warned that 'it is wrong to conclude that results must be more accurate because a technological diagnostic procedure is involved. The diagnosis of appendicitis and the differential diagnosis of abdominal pain depend on optimal clinical assessment. There is no substitute for skill in interviewing patients and eliciting physical signs. We can be sure that emphasis on technology at the expense of clinical evaluation will diminish, rather than improve, the quality of care for patients with acute abdominal pain'.

Acknowledgements

The author is grateful to Dr Elizabeth Stockdale and Mrs Claire Lyon for expert advice on radiation dosages.

References

1 Fitz RH. Perforating inflammation of the vermiform appendix; with special reference to its early diagnosis and treatment. *Am J Med Sci* 1886; **92:** 321–46.

2 Riddell JS. Appendicitis. *Scott Med Surg J* 1900; **6:** 214–22.

3 Lett H. The present position of acute appendicitis and its complications. *Lancet* 1914; **i:** 295–302.

4 Gilmour IEW, Lowdon AGR. Acute appendicitis. *Edinb Med J* 1952; **59:** 361–73.

5 Malt RA. The perforated appendix. *N Engl J Med* 1986, **315:** 1546–7.

6 Registrar General for Scotland. *Registrar General for Scotland Annual Report 1995.* Edinburgh· General Register Office, 1996.

7 Heafield R, Roe AM, Watkins R, Brodribb AJM, Brown C. Outcome of emergency surgical admissions for non-specific abdominal pain *Gut* 1990; **31:** A1167 (Abstract).

8 Korner H, Sondenaa K, Soreide JA, Andersen E, Nysted A, Lende TH. Structured data collection improves the diagnosis of acute appendicitis. *Br J Surg* 1998; **85:** 341–4.

9 Rao PM, Rhea JT, Rattner DW, Venus LG, Novelline RA. Introduction of appendiceal CT: impact on negative

appendectomy and appendiceal perforation rates. *Ann Surg* 1999; **229:** 344–9.

10 Jones PF. Acute abdominal pain in childhood, with special reference to cases not due to acute appendicitis. *BMJ* 1969; **i:** 284–6.

11 Rang EH, Fairbairn AS, Acheson ED. An enquiry into the incidence and prognosis of undiagnosed abdominal pain treated in hospital. *Br J Prev Soc Med* 1970; **24:** 47–51.

12 de Dombal FT, Leaper DJ, Staniland JR, McCann AP, Horrocks JC. Computer-aided diagnosis of acute abdominal pain. *BMJ* 1972; **ii:** 9–13.

13 de Dombal FT. The OMGE Acute Abdominal Pain Survey – progress report, 1982. *Scand J Gastroenterol* 1984; **19**(Suppl 95): 28–40.

14 Gray DWR, Collin J. Non-specific abdominal pain as a cause of acute admission to hospital. *Br J Surg* 1987; **74:** 239–42.

15 Jones PF. Active observation in the management of acute abdominal pain in children. *BMJ* 1976; **ii:** 551–3.

16 Jones PF, Bagley FH. Acute appendicitis. In: Jones PF, Krukowski ZH, Youngson GG, eds. *Emergency Abdominal Surgery*. 3rd ed. London: Chapman and Hall, 1998: 36–81.

17 White JJ, Santillana M, Haller JH. Intensive in-hospital observation: a safe way to decrease unnecessary appendicectomy. *Am Surg* 1975; **41:** 793–8.

18 O'Donnell B. *Abdominal Pain in Children*. Oxford: Blackwell Scientific Publications, 1985.

19 Thomson HJ, Jones PF. Active observation in acute abdominal pain. *Am J Surg* 1986; **152:** 522–5.

20 Dolgin SE, Beck AR, Tartter PI. The risk of perforation when children with possible appendicitis are observed in the hospital. *Surg Gynecol Obstet* 1992; **175:** 320–4.

21 Driver CP, Youngson GG. Acute abdominal pain in children: a 25 year comparison. *Health Bull (Edinb)* 1995; **53:** 167–72.

22 Senbanjo RO. Management of patients with equivocal signs of appendicitis. *J R Coll Surg Edinb* 1997; **42:** 85–8.

23 Bachoo P, Mahomed AA, Ninan GK, Youngson GG. Acute appendicitis. The continuing role for active observation. *Pediatr Surg Int* 2001; **17:** 125–8.

24 Colson M, Skinner KA, Dunnington G. High negative appendectomy rates are no longer acceptable. *Am J Surg* 1997; **174:** 723–6.

25 Bergeron E, Richer B, Gharib R, Giard A. Appendicitis is a place for clinical judgement. *Am J Surg* 1999; **177:** 460–2.

26 Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: a critical review of diagnosis and treatment in 1000 cases. *Arch Surg* 1975; **110:** 677–84.

27 Andersson RE, Hugander A, Thulin AJG. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendicectomy rate. *Eur J Surg* 1992; **158:** 37–41.

28 Walker SJ, West CR, Colmer MR. Acute appendicitis: does removal of a normal appendix matter, what is the value of diagnostic accuracy and is surgical delay important? *Ann R Coll Surg Engl* 1995; **77:** 358–63.

29 McLean AD, Stonebridge PA, Bradbury RW, Rainey JB, MacLeod DAD. Time of presentation, time of operation, and unnecessary appendicectomy. *BMJ* 1993; **306:** 307.

30 Surana R, Quinn F, Puri P. Is it necessary to perform appendicectomy in the middle of the night in children? *BMJ* 1993; **306:** 1168.

31 Jackson RH. Parents, family doctors, and acute appendicitis in childhood. *BMJ* 1963; **ii:** 277–81.

32 Moss JG, Barrie JL, Gunn AA. Delay in surgery for acute appendicitis. *J R Coll Surg Edinb* 1985; **30:** 290–3.

33 Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. *Ann Surg* 1995; **221:** 278–81.

34 Koepsell TD, Inui TS, Farewell VT. Factors affecting perforation in acute appendicitis. *Surg Gynecol Obstet* 1981; **153:** 508–10.

35 de Dombal FT, Matharu SS, Staniland JR, Wilson DH, Macadam WAF, Gunn AA *et al.* Presentation of cancer to hospital as 'acute abdominal pain'. *Br J Surg* 1980; **67:** 413–16.

36 Chang FC, Hogle HH, Welling DR. The fate of the negative appendix. *Am J Surg* 1973; **126:** 752–4.

37 Deutsch AA, Shani N, Reiss R. Are some appendicectomies unnecessary? An analysis of 319 white appendices. *J R Coll Surg Edinb* 1983; **28:** 35–40.

38 Jerman RP. Removal of the normal appendix: the cause of serious complications. *Br J Clin Pract* 1969; **23:** 466–7.

39 Sugarbaker PH, Sanders JH, Bloom BS, Wilson RE. Preoperative laparoscopy in diagnosis of acute abdominal pain. *Lancet* 1975; **i:** 442–5.

40 Deutsch AA, Zelikovsky A, Reiss R. Laparoscopy in the prevention of unnecessary appendicectomies: a prospective study. *Br J Surg* 1982; **69:** 336–7.

41 Mutter D, Vix M, Bui A, Evrard S, Tassetti V, Breton JF *et al.* Laparoscopy not recommended for routine appendectomy in men: results of a prospective randomized study. *Surgery* 1996; **120:** 71–4.

42 van den Broek WT, Bijnen AB, de Ruiter P, Gouma DJ. A normal appendix found during diagnostic laparoscopy should not be removed. *Br J Surg* 2001; **88:** 251–4.

43 Grunewald B, Keating J. Should the 'normal' appendix be removed at operation for appendicitis? *J R Coll Surg Edinb* 1993; **38:** 158–60.

44 Parkes SE, Muir KR, al Sheyyab M, Cameron AH, Pincott JR, Raafat F *et al.* Carcinoid tumours of the appendix in children 1957–1986: incidence, treatment and outcome. *Br J Surg* 1993; **80:** 502–4.

45 Decadt B, Sussman L, Lewis MPN, Secker A, Cohen L, Rogers C *et al.* Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain. *Br J Surg* 1999; **86:** 1383–6.

46 Douglas CD, Macpherson NE, Davidson PM, Gani JS. Randomised controlled trial of ultrasonography in diagnosis of acute appendicitis, incorporating the Alvorado score. *BMJ* 2000; **321:** 919–22.

47 Davies AH, Mastorakou I, Cobb R, Rogers C, Lindsell D, Mortensen NJMcC. Ultrasonography in the acute abdomen. *Br J Surg* 1991; **78:** 1178–80.

48 Birnbaum BA, Wilson SR. Appendicitis at the millennium. *Radiology* 2000; **215**: 337–48.

49 Weyant MJ, Eachempati SR, Maluccio MA, Rivadeneira DE, Grobmeyer SR, Hydo LJ *et al* Interpretation of computed tomography does not correlate with laboratory or pathologic findings in surgically confirmed acute appendicitis. *Surgery* 2000; **128**: 145–52.

50 Stroman DL, Bayouth CV, Kuhn JA, Westmoreland M, Jones RC, Fisher TL *et al* The role of computed tomography in the diagnosis of acute appendicitis. *Am J Surg* 1999; **178**: 485–9.

51 Peck J, Peck A, Peck C, Peck J. The clinical role of noncontrast helical computed tomography in the diagnosis of acute appendicitis. *Am J Surg* 2000; **180**: 133–6.

52 Wall BF, Hart D. Revised radiation doses for typical x-ray examinations. Report on a recent review of doses to patients from medical x-ray examinations in the UK by NRPB. National Radiological Protection Board. *Br J Radiol* 1997; **70**: 437–9.

53 Donnelly LF, Emery KH, Brody AS, Laor T, Gylys-Morin VM, Anton CG *et al.* Minimizing radiation dose for pediatric body applications of single-detector helical CT. strategies at a large Children's Hospital. *AJR Am J Roentgenol* 2001; **176**: 303–6.

54 Schwartz SI. Tempering the technological diagnosis of acute appendicitis. *N Engl J Med* 1987; **317**: 703–4.

Randomized clinical trial of patient-controlled *versus* fixed regimen feeding after elective abdominal surgery

I. J. M. Han-Geurts, J. Jeekel, H. W. Tilanus and K. J. Brouwer*

Departments of Surgery, Erasmus University Medical Centre and *Medical Centre Rijnmond Zuid, location Zuider, Rotterdam, The Netherlands
Correspondence to: Dr I. J. M. Han-Geurts, Department of Surgery, University Hospital Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands (e-mail: Capel@hlkd.azr.nl)

Background: Although studies have shown that early oral feeding after abdominal surgery is feasible, many surgeons still advocate a careful, slow introduction of postoperative oral feeding. This study was conducted to investigate whether patient-controlled postoperative feeding is possible in patients undergoing colonic or aortic surgery.

Methods: A randomized clinical trial compared patient-controlled postoperative oral feeding (PC group) with a fixed regimen (FR group). Patients in the PC group ($n = 56$) received oral feeding when they requested it; patients in the FR group ($n = 49$) started a normal diet on day 5. Endpoints were time to tolerance of a diet similar to the preoperative diet, reinsertion of a nasogastric tube, complications and duration of hospitalization.

Results: Median time to resumption of a normal diet was 3 days in the PC group and 5 days in the FR group ($P < 0.001$). Reinsertion of a nasogastric tube was required in nine patients in each group (P not significant). The incidence of complications was similar in both groups: 12 of 56 in the PC group and 13 of 49 in the FR group. There was no significant difference in duration of hospital stay between the groups.

Conclusion: Most patients tolerate a normal diet on the third day after operation. Patient-controlled postoperative feeding is safe and leads to earlier resumption of a normal diet.

Paper accepted 13 August 2001

British Journal of Surgery 2001, **88**, 1578–1582

Introduction

Postoperative nutritional status is a major factor in clinical outcome[1–5]. Most surgeons use a regimen in which oral feeding is gradually introduced following the resumption of bowel sounds and the passage of flatus. This policy is based mainly on fear of anastomotic leakage and persisting ileus. Postoperative paralytic ileus is due to inhibitory neural reflexes in the gastrointestinal tract and to local release of inflammatory agents[6,7]. Various factors influence the duration of postoperative ileus, the most important being the nature of the surgery[8]. There are indications that resumption of enteral feeding is one of the factors that diminishes the duration of ileus[9].

Several small prospective clinical trials have questioned the policy of a gradual introduction of postoperative diet and have concluded that early oral feeding is feasible[10–14]. In these studies resumption of eating took place either after the nasogastric tube had been removed or on the second day after operation, as desired by the patient.

Patient-controlled feeding after operation may lead to a better nutritional status and to an earlier feeling of well-being than feeding according to a fixed regimen. The former may thus promote earlier hospital discharge. This hypothesis was investigated in a prospective randomized trial comparing postoperative patient-controlled feeding with a fixed regimen.

Patients and methods

In a 1-year period 105 patients awaiting elective abdominal surgery were randomized to participate in the trial (*Table 1*). Randomization took place in the operating theatre preceding operation. All 105 patients were enrolled in the study and underwent elective abdominal surgery including open colonic surgery and transabdominal central vascular reconstruction procedures. They were all above the age of 18 years and were not participating in another study at that time. Furthermore, all patients were mentally competent, able to speak and understand the Dutch language, and gave written informed consent. The study was approved by the medical ethics committee.

Patients were assigned randomly to a patient-controlled diet after operation (PC group) or a fixed postoperative feeding regimen (FR group). Randomization was by the use of sequentially numbered, sealed envelopes. Patients in the PC group chose when to start an oral diet. The feeding regimen for the FR group was as follows: 25 ml water per h on the day of operation (day 0); 50 ml water per h on day 1; liquid diet consisting of water, tea, coffee and lemonade on day 2; liquid diet on day 3; easily digestible diet on day 4; and normal diet on day 5.

All operations were performed by a consultant surgeon or a senior resident supervised by a consultant surgeon. All patients underwent mechanical bowel preparation before operation. A nasogastric tube was inserted before surgery and was removed immediately after the operation in each patient.

Outcome measures were the time span between operation and the tolerance of a normal diet, reinsertion of a nasogastric tube, complications and duration of hospital stay. Postoperative complications related to the type of surgery were defined and registered. Anastomotic leakage was assessed by clinical symptoms or radiological examination. Ileus was assessed by clinical examination. The length of hospitalization, defined as the number of days in hospital after the day of the operation, was recorded. Patients were discharged when able to tolerate a normal diet, had had a bowel movement and had no complications preventing hospital discharge. During their admission, patients were asked several questions concerning nausea, vomiting, flatus, bowel movement and diet, and their responses were recorded in a diary. Reinsertion of a nasogastric tube was recorded. Two clinical investigators examined the patients daily, listened for bowel sounds and supervised completion of the diaries. In addition, patients noted their preferences on standard hospital dietary forms. The clinician responsible for the clinical decisions regarding treatment also examined the patients.

Table 1 Baseline patient characteristics

	PC group ($n = 56$)	FR group ($n = 49$)
Sex ratio (M : F)	25 : 31	32 : 17
Age (years)*	68(12)	65(12)
Type of surgery		
Vascular	38	30
Colonic	18	19

*Values are mean(s.d.). PC, patient controlled; FR, fixed regimen

Statistical analysis

All randomized patients were analysed on an intention-to-treat basis. Continuous, normally distributed data are expressed as mean(s.d.) and other quantitative data as median (range). The Mann–Whitney *U* test was used to compare non-normally distributed data between study groups. The χ^2 test was used to compare proportions. *P* values reported are two-tailed. $P < 0{\cdot}05$ was considered to be statistically significant.

Results

Over 1 year 105 patients were randomized and included in the trial. Patient characteristics were comparable between the two groups (*Table 1*).

There were two cases of anastomotic leakage in the PC group, both in patients who had a colonic resection. One anastomotic leak occurred in the FR group. These three patients required reoperation. Other complications occurred in ten patients in the PC group and 12 patients in the FR group (*Table 2*). There were three deaths, all in the PC group ($P < 0{\cdot}05$). One patient died 3 days after operation from a myocardial infarction; another patient developed fatal acute respiratory distress syndrome 2 days after operation. There were no signs of aspiration. Neither patient had resumed a solid diet at that time and it is improbable that these deaths were related to food intake. The third patient developed postoperative ischaemic colitis following aortic surgery The patient underwent a Hartmann's procedure but died from multiple organ failure.

Table 2 Number and type of complications

	PC group ($n = 56$)	FR group ($n = 49$)
Relaparotomy		
Anastomotic leakage*	2	1
Postoperative haemorrhage	1	1
Other†	3	1
Pelvic abscess	0	1
Myocardial infarction	1	1
Stroke	0	1
Pneumonia	1	1
Urinary tract infection	2	4
Wound infection	0	2
Exacerbation COPD	1	0
Asthma cardiale	1	0
Total	12	13

No patient had more than one complication. *Colonic surgery only; †prolonged ileus, colitis. PC, patient controlled; FR, fixed regimen; COPD, chronic obstructive pulmonary disease

Nine patients in each group required reinsertion of a nasogastric tube because of repeated vomiting. In each case the tube was withdrawn the next day and oral feeding was resumed according to randomization. All other patients tolerated their diet well. Median duration to resumption of a normal diet was 3 days in the PC group compared with 5 days in the FR group ($P < 0{\cdot}001$). The median duration of hospital stay was 11 days in both groups (P not significant) (*Table 3*).

A comparison was made between patients undergoing aortic surgery and those undergoing colonic surgery with respect to hospital stay and time to resumption of a normal diet. In neither group was a significant difference found (*Table 4*).

There were no significant differences between the FR and PC groups in the incidence of nausea and vomiting, and time to passage of flatus and faeces. All patients in both groups had bowel movement on the first day after operation.

Discussion

Several aspects of postoperative management in general surgery are more empirical than evidence based. One example is the standard use of a nasogastric tube peroperatively and after surgery. In several studies it has been shown that this does not contribute to a better recovery and often leads to complications such as aspiration[15–17]. Another example is the belief that patients should not eat until a few days after surgery, in order to avoid anastomotic leakage or ileus. Several small prospective randomized studies have demonstrated that this strict feeding regimen is not necessary. Bufo *et al.*[10] concluded that most patients tolerated immediate postoperative feeding without developing major complications; these findings were confirmed by several others[12–15,18–21]. However, in most of these latter studies the nasogastric tube was only removed following bowel movement[11,12,14,18], or a regular diet was started only several days after surgery[10,13,19,20].

In the present study a normal diet was tolerated in nearly all patients in the PC group 3 days after operation. In all cases the nasogastric tube was removed directly after surgery. Reinsertion occurred nine times in both groups; these results are similar to those of previous reports[11,13,22,23]. In contrast to the aforementioned studies, patients were given the opportunity to start a normal diet on the first postoperative day. In other studies a regular diet was resumed a few days after surgery on the assumption that postoperative ileus takes 24–48 h to resolve. However, Avrahami *et al.*[24], studying gastric emptying after transabdominal vascular surgery, concluded that a normal diet may be started on the second day after operation. In the present study all patients started fluids on the first postoperative day. The median time to resumption of a normal diet in the PC group was 3 days in contrast to 5 days in the FR group. There was no difference between the groups in the need for reinsertion of a nasogastric tube. These findings justify the conclusion that patients are able to judge their own food tolerance adequately.

There was no difference in time to resumption of a normal diet between patients who underwent aortic surgery and those who had colonic surgery in either group. Although the number of patients was was small, these results are in accordance with other reports[24,25].

The incidence of anastomotic leakage and overall complications did not differ from that in other reports. The size of the group was too small to relate anastomotic leakage to a feeding regimen. Experimental studies have shown that anastomotic healing in rats is improved by early postoperative enteral feeding[26]; clinical studies, however, lacked sufficient patient numbers to confirm these findings.

Table 3 Primary outcome measures

	PC group	FR group
Time to normal diet (days)	3 (1–12)	5 (4–13)*
Hospital stay (days)	11 (3–72)	11 (6–34)

Values are median (range). PC, patient controlled; FR, fixed regimen. *$P < 0{\cdot}001$ *versus* PC group (Mann–Whitney U test)

Table 4 Time to resumption of normal diet and hospital stay in patients who underwent aortic and colonic surgery

	PC group		FR group	
	Aortic	Colonic	Aortic	Colonic
Time to normal diet (days)	5 (2–12)	4 (1–11)	6 (4–9)	6 (4–13)
Hospital stay (days)	13 (7–35)	15 (3–72)	12 (6–34)	12 (6–27)

Values are mean (range). PC, patient controlled; FR, fixed regimen. There were no significant differences between patients who had aortic or colonic surgery in either group

Duration of recovery may be influenced positively by an early feeding regimen and may lead to earlier discharge from hospital. The duration of hospitalization was not shorter in the PC group in the present study, whereas a trend towards a shorter hospital stay has been observed previously when an early feeding regimen is followed[27–29].

Secondary endpoints did not differ between groups. The importance of bowel movement as an indicator for regaining bowel function is questionable as it also represents activity of the small bowel. Passage of flatus and stool is often used as a measure of resolving postoperative ileus. However, both are non-specific since they may only indicate distal bowel emptying. Furthermore, duration of postoperative ileus is influenced by many different factors. The present findings confirm the assumption that these subjective measures of bowel function cannot indicate when to start or expand an oral diet.

It is concluded that patient-controlled postoperative feeding is safe and is started significantly earlier than the fixed regimen imposed by the physician.

References

1 Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA *et al.* Enteral *versus* parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg* 1991; **215:** 503–13.

2 Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB *et al.* Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. *Ann Surg* 1992; **216:** 172–83.

3 Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. *Gut* 1996; **39:** 833–5.

4 Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Carlo VD. Immune and nutritional effects of early enteral nutrition after major abdominal operations. *Eur J Surg* 1996, **162:** 105–12

5 Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P *et al.* Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* 1997; **132:** 1222–30.

6 Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. *Ann Surg* 1998; **228:** 652–63.

7 Kalff JC, Buchholz BM, Eskandari MK, Hierholzer C, Schraut WH, Simmons RL *et al.* Biphasic response to gut manipulation and temporal correlation of cellular infiltrates and muscle dysfunction in rat. *Surgery* 1999; **126:** 498–509.

8 Shibata Y, Toyoda S, Nimura Y, Miyati M. Patterns of intestinal motility recovery during the early stage following abdominal surgery: a clinical and manometric study. *World J Surg* 1997, **21:** 806–9.

9 Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. *Aust N Z J Surg* 1998; **68:** 125–8.

10 Bufo AJ, Feldman S, Daniels GA, Lieberman RC. Early postoperative feeding. *Dis Colon Rectum* 1994; **37:** 1260–5.

11 Bickel A, Shtamler B, Mizrahi S. Early oral feeding following removal of nasogastric tube in gastrointestinal operations A randomized prospective study. *Arch Surg* 1992; **127:** 287–9.

12 Jeffery KM, Harkins B, Cresci GA, Martindale RG. The clear liquid diet is no longer a necessity in the routine postoperative management of surgical patients. *Am Surg* 1996, **62:** 167–70.

13 Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* 1995, **222:** 73–7.

14 Ortiz H, Armendariz P, Yarnoz C. Is early postoperative feeding feasible in elective colon and rectal surgery? *Int J Colorectal Dis* 1996; **11:** 119–21.

15 Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective *versus* routine nasogastric decompression after elective laparotomy. *Ann Surg* 1995; **221:** 469–78.

16 Nathan BN, Pain JA. Nasogastric suction after elective abdominal surgery: a randomised study. *Ann R Coll Surg Engl* 1991; **73:** 291–4.

17 Petrelli NJ, Stulc JP, Rodriguez-Bigas M, Blumenson L. Nasogastric decompression following elective colorectal surgery: a prospective randomised study. *Am Surg* 1993; **59:** 632–5.

18 Ray SA, Rainsbury RM. Patient tolerance of the early introduction of oral fluids after laparotomy *Ann R Coll Surg Engl* 1993; **75:** 157–60.

19 Carr CS, Ling KD, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. *BMJ* 1996; **312:** 869–71.

20 Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW *et al.* A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg* 1997; **226:** 567–80.

21 Ortiz H, Armendariz P, Yarnoz C. Early postoperative feeding after elective colorectal surgery is not a benefit unique to laparoscopy-assisted procedures. *Int J Colorectal Dis* 1996, **11:** 246–9

22 Hartsell PA, Frazee RC, Harrison JB, Smith RW. Early postoperative feeding after elective colorectal surgery. *Arch Surg* 1997; **132:** 518–21.

23 Detry R, Ciccarelli O, Komlan A, Claeys N. Early feeding after colorectal surgery Preliminary results. *Acta Chir Belg* 1999; **99:** 292–4.

24 Avrahami R, Cohen JD, Haddad M, Singer P, Zelikovski A. Gastric emptying after elective abdominal aortic aneurysm

surgery: the case for early postoperative enteral feeding. *Eur J Vasc Endovasc Surg* 1999; **17:** 241–4.
25 Podore PC, Throop EB. Infrarenal aortic surgery with a 3-day hospital stay. A report on success with a clinical pathway. *J Vasc Surg* 1999; **29:** 787–92.
26 Demetriades H, Botsios D, Kazantzidou D, Sakkas L, Tsalis K, Manos K *et al.* Effect of early postoperative enteral feeding on the healing of colonic anastomoses in rats. Comparison of three different enteral diets. *Eur Surg Res* 1999; **31:** 57–63.
27 Binderow SR, Cohen SM, Wexner SD, Nogueras JJ. Must early postoperative oral intake be limited to laparoscopy? *Dis Colon Rectum* 1994; **37:** 584–9.
28 Hawalsi A, Schroder DM, Lloyd LR, Featherstone R. Elective conventional colectomy in the era of laparoscopic surgery. *Am Surg* 1996; **62:** 589–93.
29 Di Fronzo LA, Cymerman J, O'Connell TX. Factors affecting early postoperative feeding following elective open colon resection. *Arch Surg* 1999; **134:** 941–6.

If you wish to comment on this, or any other article published in the *BJS*, please visit the on-line correspondence section of the website (www.bjs.co.uk). Electronic communications will be reviewed by the Correspondence Editor and a selection will appear in the correspondence section of the Journal. Time taken to produce a thoughtful and well written letter will improve the chances of publication in the Journal.

Original article

Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery

J. I. Spark and D. J. A. Scott

Department of Vascular Surgery, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK
Correspondence to: Mr J. I. Spark, Flat 4, 23 Stainbeck Lane, Chapel Allerton, Leeds LS7 3QR, UK (e-mail: jamesianspark@hotmail.com)

Introduction: There is evidence to suggest that the polymorphonuclear neutrophil (PMN) plays a critical early step in the development of the ischaemia–reperfusion syndrome, the systemic inflammatory response syndrome (SIRS) and sepsis. The PMN receptor CD16 plays an important role in phagocytosis, cell-mediated cytotoxicity and the release of free radicals and proteolytic enzymes. The aim of this study was to determine whether there is any relationship between PMN CD16 expression, phagocytosis and the development of sepsis.

Methods: Fifty patients who underwent elective infrarenal abdominal aortic aneurysm repair were studied. Venous blood was taken before operation, throughout surgery and for 7 days after operation. CD16 expression was measured, unstimulated and following further stimulation, by means of flow cytometry. Phagocytosis was determined using flow cytometry.

Results: Some 36 patients had an uncomplicated recovery; 14 developed SIRS or sepsis. There was no difference between the two groups with respect to nutritional, co-morbid or technical factors. In the group that developed septic complications after operation, the level of PMN CD16 expression was significantly higher before surgery (mean channel fluorescence (MCF) 30·2 *versus* 10·4; $P < 0{\cdot}05$, Mann–Whitney *U* test) and throughout the postoperative period. Surgery produced no change in CD16 expression. After operation, stimulation of PMNs in the septic group resulted in a fall in CD16 expression (40·8 *versus* 20·4 MCF; $P < 0{\cdot}05$, Mann–Whitney *U* test); surgery produced no change in the level of expression in the uncomplicated group.

Conclusion: This study provides evidence of phenotypic and functional differences in neutrophil behaviour in patients who develop sepsis following aneursym surgery.

Paper accepted 16 July 2001

British Journal of Surgery 2001, 88, 1583–1589

Introduction

The incidence of postsurgical sepsis has remained unchanged over the past decade[1], despite improved management before and after operation, and ever more potent antibiotic prophylaxis. This raises the possibility that, at least as far as surgical infection is concerned, other factors are important. This may include the existence of an idiosyncratic susceptibility of some individuals to the development of postoperative sepsis.

The neutrophil represents the first line in the non-specific host defence against a wide range of pathogens. When invading micro-organisms are opsonized with immunoglobulins and complement fragments, the neutrophil will recognize and bind these particles through its Fc and complement receptors. This results in neutrophil activation followed by phagocytosis and killing of the pathogen. Human neutrophils express two types of low-affinity receptor for IgG: FcγRIIa (CD32) and FcγRIIIb (CD16)[2–5].

Upon stimulation of neutrophils with phorbol 12-myristate 13-acetate (PMA) or during chemotaxis or apoptosis, FcγRIIIb is shed from the cell surface by proteolytic cleavage[6]. It is currently not known how this proteolytic event is regulated. Studies with protease inhibitors have indicated that many cellular membrane proteins can be shed by (matrix) metalloproteinases[7,8]. However, FcγRIIIb shedding is inhibited not only by metalloproteinase inhibitors, but also by serine protease inhibitors[9,10].

In addition to the functionally important molecular configuration of CD16 on neutrophils, two allelic polymorphisms have been described, the *NA1/NA2* polymorphisms[11]. Individuals homozygous for the *NA2* allele are less efficient in phagocytosis of opsonized micro-organisms. As allelic polymorphisms of neutrophil CD16 are associated with functional differences in neutrophil activity, their study may provide an insight into the nature of the biological variation that leads some individuals to develop sepsis after operation whereas, under identical conditions, others do not.

The aim of the present study was to determine whether there is any relationship between neutrophil CD16 receptor expression, phagocytosis and development of the systemic inflammatory response sydrome (SIRS) or sepsis.

Patients and methods

The protocol used in the study was approved by the local ethics committee. Consecutive patients undergoing elective abdominal aortic aneurysm (AAA) repair at St James's University Hospital were studied; demographic details were recorded according to criteria laid down by the Society of Vascular Surgery and the International Society of Cardiovascular Surgery.

The patients were matched as far as possible. Identical grafts (Haemashield; Meadox, Caddington, UK) were used in all operations. The heparin protocol was identical throughout the study: 5000 units heparin were given intravenously 3 min before aortic cross-clamping.

The general anaesthetic was standard. Induction was with propofol and tracrium, and anaesthesia was maintained with nitrous oxide, oxygen and enflurane. Epidural anaesthesia was used where possible.

Aneurysms were repaired in a standard fashion with either a tube or a bifurcated graft.

Antibiotic prophylaxis consisted of 1·5 g cefuroxime and 500 mg metronidazole on induction, followed by a further two postoperative doses.

Peripheral venous blood samples were obtained before, during and after operation for the first 7 days. Paired samples were obtained from both venous and arterial lines in a subgroup of patients to study possible variation due to sample source. Blood was drawn slowly into polythene syringes, decanted into devacuumed Vacutainer tubes and transported to the laboratory on melting ice.

The development of sepsis and SIRS, as defined by the American College of Chest Physicians and the Society of Critical Care Medicine (*Table 1*)[12], was recorded.

Table 1 American College of Chest Physicians and Society of Critical Care Medicine definitions of systemic inflammatory response syndrome and sepsis[12]

SIRS	Signs of a systemic response (two of the following):
	Fever or hypothermia (core or rectal temperature greater than 38·4°C or less than 35·6°C)
	Tachycardia (heart rate above 90 beats per min)
	Tachypnoea (respiration greater than 20 breaths per min)
	White blood cell count greater than 12×10^9/l or less than 4×10^9/l
Sepsis	Presence of SIRS associated with an infectious process

SIRS, systemic inflammatory response syndrome

Measurement of CD11b/16 expression

A 100-µl sample of anticoagulated venous blood was incubated with 5 µl of an anti-CD16 mouse monoclonal antibody prelabelled with a fluorescent dye, phycoerythrin (red) (Becton Dickinson, Oxford, UK) and incubated at room temperature (18–23°C) for 30 min. A control was set up simultaneously with 5 µl of a non-specific antibody labelled with a phycoerythrin dye.

Measurement of CD16 expression was performed with a flow cytometer (Epics-XL; Coulter Electronics, Fullerton, California, USA) using acquisition software (XL; Coulter Electronics). The granulocyte population in the samples was identified from patterns of forward and 90° light scattering, and these signals were used for gating so that fluorescent signals from neutrophils alone were analysed. Frequency distributions of the intensity of fluorescence from individual cells were collected. The median channel number was determined for each sample. The intensity of fluorescence for neutrophils labelled with the specific antibody was determined relative to the intensity of fluorescence for cells labelled with a non-specific antibody.

CD16 expression following stimulation

To investigate whether surgery or ischaemia–reperfusion affected the subsequent ability of neutrophils to respond to further stimuli (a 'second hit') the cells were first stimulated and then CD16 expression was measured. A 100-µl sample of blood from each timepoint was incubated with phosphate-buffered saline (control), PMA at a final concentration of 100 ng/ml, and *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) at a final concentration of 10^{-6} mol/l for 30 min at 37°C in a shaking water bath. CD16 expression was subsequently measured by means of flow cytometry.

Neutrophil phagocytosis

Neutrophil phagocytosis was quantified using the commercially available Phagotest® (Orpegen Pharma, Hannover, Germany).

Measurement of neutrophil phagocytosis was performed with the Epics-XL flow cytometer. The granulocyte population was gated on as before, using patterns of forward and 90° light scattering. The percentage of cells that performed phagocytosis as well as their mean fluorescence intensity (number of ingested bacteria) were analysed. For this, a region of interest was set on the green fluorescent cells for comparison against the assay control at 0°C to determine the percentage of phagocytosing cells. The mean fluorescence correlated with the number of bacteria per single leucocyte.

Statistical analysis

The study generated a large amount of data that was recorded on a pro forma and transferred to Microsoft Excel version 7.0 (Microsoft Corporation, Grove City, Ohio, USA). Statistical analyses were performed using the Excel add-in, Astute (University of Leeds, Leeds, UK) and C-Stat for Windows (Cherwell Scientific, Oxford, UK). As the data were skewed, non-parametric analyses were employed. The results were expressed as median (interquartile range). Differences in the distribution of a variable between the groups were estimated by means of the χ^2 test with Yates' correction or Fisher's exact test, where appropriate. The Mann–Whitney *U* test of significance was used to examine differences between results in the two groups, with the Wilcoxon signed rank test being used to test for differences within the same group. Analysis of variance was used to assess the immunological parameters over the course of the study.

Results

Fifty consecutive patients undergoing AAA repair were studied; there were 39 men and 11 women with a median age of 72 (range 54–84) years.

Thirty-six patients made an uncomplicated recovery, but 14 developed sepsis or SIRS. There were no significant demographic differences between patients in the two groups, and all had similar risk factors for vascular disease (*Table 2*).

One patient was returned to theatre because of a proximal anastomotic leak, and sustained a myocardial infarction immediately after operation. This patient developed adult respiratory distress syndrome and renal failure, and died on the tenth postoperative day. Other complications included seven chest infections; one patient had an ischaemic sigmoid colon that required resection and subsequently developed a wound infection, and a second patient had a groin wound infection. Four other patients developed SIRS.

CD16 results

Early in the study, simultaneous blood sampling from arterial and venous sites was performed in ten patients at all timepoints. Analysis of neutrophil CD16 in these samples showed no site-dependent (i.e. arterial *versus* venous) differences.

Table 2 Characteristics of 50 patients who had aortic aneurysm surgery

	Uncomplicated recovery ($n = 36$)	SIRS or sepsis ($n = 14$)
Sex ratio (M : F)	28 : 8	11 : 3
Age (years)*	72 (54–82)	70 (54–84)
Smoker	26	11
Pulmonary disease	7	4
Renal disease	3	1
Diabetes	3	1
Ischaemic heart disease	21	9
Hypertension	19	8
Cerebrovascular disease	5	2
Aortic cross-clamp time (min)*	40 (35–60)	45 (27–55)
Length of anaesthesia (min)*	150 (120–240)	145 (135–225)
Blood loss (ml)*	800 (500–2800)	1500 (500–3045)

*Values are median (interquartile range). SIRS, systemic inflammatory response syndrome

During the course of the operation CD16 expression fell from a mean channel fluorescence (MCF) of 20·4 to a minimum of 14·4 MCF on the first postoperative day, although this was not statistically significant ($P > 0·05$, Wilcoxon matched pairs test).

When the patients were classified according to whether they developed SIRS, the level of CD16 expression was higher before operation in patients with infective complications than in those who had an uncomplicated recovery (30·2 *versus* 10·4 MCF; $P < 0·01$, Mann–Whitney *U* test). The level of CD16 expression remained higher throughout the operative and postoperative interval ($P < 0·05$, two-way analysis of variance between groups) in the patients with SIRS or sepsis (*Fig. 1*).

Stimulated expression

To investigate whether the operation or ischaemia–reperfusion insult affected the subsequent ability of neutrophils to mobilize CD16 to the cell surface following further stimulation (i.e. 'a second hit'), the cells were first stimulated and then CD16 expression was measured. Stimulation of the neutrophils before operation resulted in an increase in CD16 expression in both groups. After operation, stimulation of the neutrophils in patients with sepsis produced a fall in CD16 expression (40·8 *versus* 20·4 MCF on day 1; $P < 0·05$, Wilcoxon signed rank test); surgery produced no change in the level of expression in patients who made an uncomplicated recovery (*Fig. 2*). A similar result was obtained when the samples were stimulated with PMA.

Phagocytosis

There was a significant fall in the percentage of polymorphonuclear neutrophils (PMNs) phagocytosing on the first postoperative day, from 93·6 per cent before operation to 84·4 per cent ($P = 0·04$, Mann–Whitney *U* test). This fall persisted on the seventh postoperative day ($P = 0·034$, Mann–Whitney *U* test). There was, however, no difference in the percentage of PMNs phagocytosing in patients who developed an infective complication compared with those who had an uncomplicated recovery.

The number of *Escherichia coli* ingested by each neutrophil (MCF) was similar before surgery (73·4 *versus* 76·2 MCF; $P < 0·05$, Mann–Whitney *U* test), but showed a greater reduction in the septic group after operation (72·4 *versus* 39·7 MCF on day 1; $P < 0·05$, Mann–Whitney *U* test) (*Fig. 3*).

Discussion

Neutrophils participate in a range of cellular functions including phagocytosis, release of both oxygen intermediates and specific granule proteins, and antibody-dependent cell-mediated cytotoxicity. Each of these functions can be

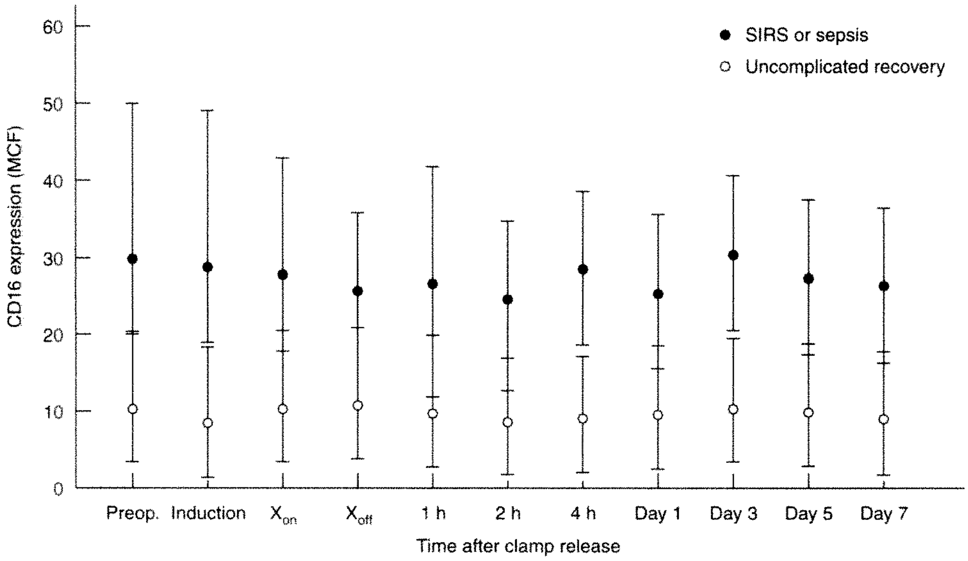
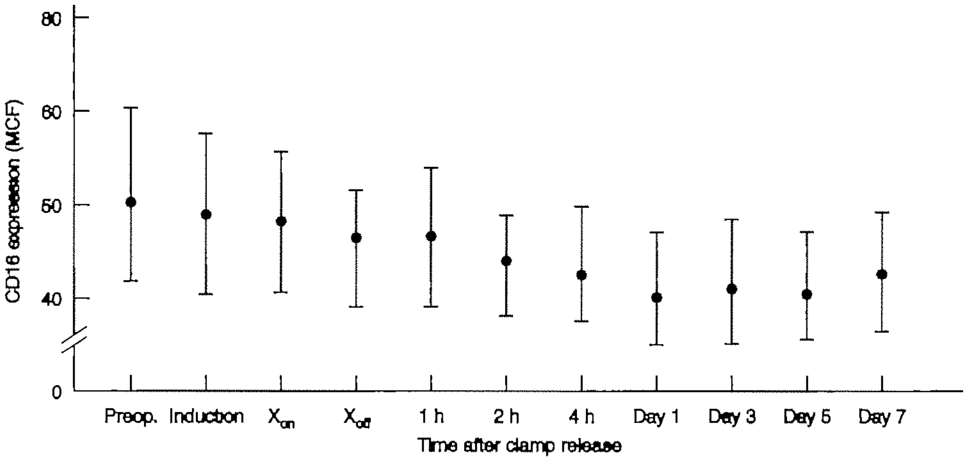
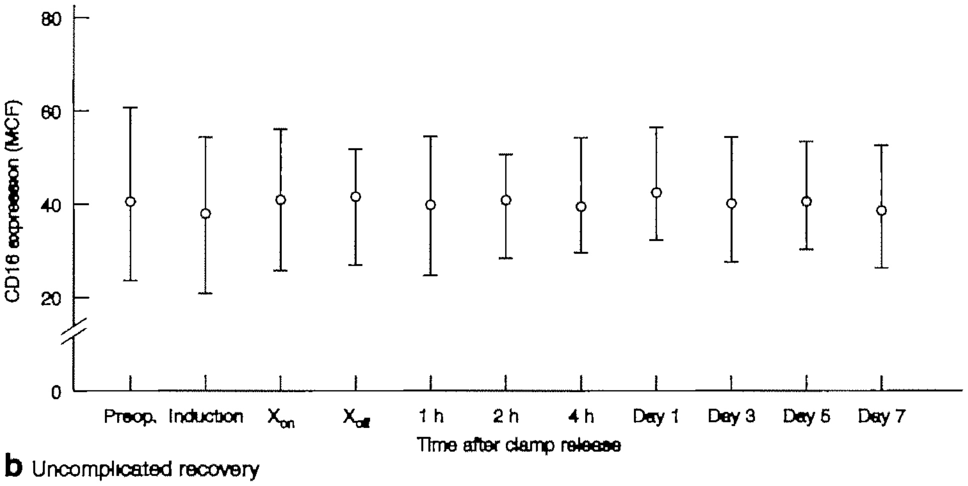


Fig. 1 Effect of aortic surgery and ischaemia–reperfusion on unstimulated CD16 expression in patients with sepsis or systemic inflammatory response syndrome (SIRS) ($n = 14$) and in those with an uncomplicated recovery ($n = 36$). Values are medians and interquartile ranges. Mean channel fluorescence (MCF) is a measure of the level of intensity of receptor expression. X_{on} and X_{off}, cross-clamp on and off



a SIRS or sepsis



b Uncomplicated recovery

Fig. 2 Effect of aortic surgery and ischaemia–reperfusion on stimulated CD16 expression following stimulation with *N*-formyl-methionyl-leucyl-phenylalanine **a** in patients with sepsis or systemic inflammatory response syndrome (SIRS) (*n* = 14) and **b** in those with an uncomplicated recovery (*n* = 36). Values are medians and interquartile ranges. Mean channel fluorescence (MCF) is a measure of the level of intensity of receptor expression. X_{on} and X_{off}, cross-clamp on and off

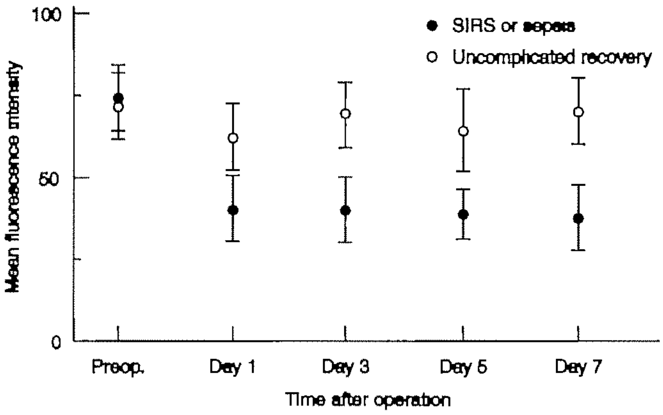


Fig. 3 Intensity of phagocytosis per neutrophil in 50 patients who had aortic aneurysm surgery and subsequently developed sepsis or systemic inflammatory response syndrome (SIRS) (*n* = 14) or made an uncomplicated recovery (*n* = 36). Values are medians and interquartile ranges

triggered by the binding of immunoglobulin (Ig) G by receptors for the constant fraction (Fc) of IgG (FcRγ).

Neutrophil (PMN) CD16 expression is a dynamic, restorative process. PMNs synthesize CD16 *de novo*, localizing it in the Golgi complex and small vesicles that transport CD16 to the plasma membrane, where they are then conjugated to their phosphatidyl-inositol-glycan anchor[13]. Thus, for any individual, the level of PMN CD16 expression depends not only on the rate of synthesis but also on the rate of release from the membrane.

The level of CD16 expression runs at a constitutively steady level in individuals and is unaltered, unlike other Fc receptors, by acute bacterial infection[14] or exposure to cytokines such as interferon γ[15]. Similarly surgery and reperfusion had no effect on PMN CD16 expression.

The peculiar anchorage of the CD16 molecule on neutrophils suggests that release of the receptor is an important process, with both cellular and humoral implications[16]. PMN activation causing the release of CD16 may be an autoregulatory process. By shedding the receptor, fewer sites are available for binding IgG, thus reducing the number of possible pathways for subsequent neutrophil activation. Alternatively it has been proposed that the release of CD16 may allow more efficient binding of IgG to CD32 (FcRγII)[17], the receptor primarily responsible for activation of the neutrophil's lytic machinery. The cleavage of CD16 from its PI-G anchor results in an increased level of cytosolic 1,2-diacylglycerol[18], an important second messenger.

A soluble CD16 has been detected in human plasma[19]. The role of such a soluble receptor is unknown, but its presence in the serum may bind to IgG and therefore interfere with the opsonization of infective organisms. It is interesting that high expressors of CD16 were individuals who tended to develop SIRS or sepsis. It may be that this is partly due to the formation of greater amounts of soluble CD16 in the changing cytokine and metabolic environment of surgery.

Although surgery had no effect on CD16 expression, stimulation with fMLP and PMA revealed that the amount of CD16 that could be mobilized to the cell surface was lower after operation than in the equivalent preoperative sample. This may be interpreted in a number of ways. It may be that surgery and/or reperfusion inhibits the normal transport process of the CD16 receptor to the cell surface. Alternatively, these findings may result from depletion of intracellular stores of PMN CD16 within the circulating leucocyte pool. If receptor transport were being influenced, it seems unlikely that the constitutive steady-state PMN surface expression of CD16 would be maintained through the postoperative period.

The fall in the number of both phagocytosing neutrophils and bacteria phagocytosed per cell supports work suggesting that some neutrophil activity is suppressed following trauma or major surgery[20,21]. The greater fall in patients with sepsis may again be related to an anomaly in the CD16 anchorage.

While it is recognized that leucocytes obtained from peripheral venous samples may represent a specific subpopulation, that is, the activated neutrophils may already have left the circulation to participate in the local inflammatory processes, this study has provided evidence of phenotypic and functional differences in neutrophil behaviour in patients who developed SIRS or sepsis following aneurysm surgery. This difference occurred early in the postoperative period and it may be possible to identify these patients before operation.

References

1 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818–29.

2 Hulett MD, Hogarth PM. Molecular basis of the Fc receptor function. *Adv Immunol* 1994; **57:** 1–127.

3 Ravetch JV, Perussia B. Alternative membrane forms of FcγRIII (CD16) on human natural killer cells and neutrophils. Cell type-specific expression of two genes that differ in single nucleotide substitutions. *J Exp Med* 1989; **170:** 481–97.

4 Ravetch JV, Kinet JP. Fc receptors. *Annu Rev Immunol* 1991; **9:** 457–92.

5 Tosi MF, Zakem H. Surface expression of Fc gamma receptor III (CD16) on chemoattractant-stimulated neutrophils is determined by both surface shedding and translocation from intracellular storage compartments. *J Clin Invest* 1992; **90:** 462–70.

6 Moldovan I, Galon J, Maridonneau-Parini I, Roman Roman S, Mathiot C, Fridman W-H *et al.* Regulation of production of soluble Fcgamma receptors type III in normal and pathological conditions. *Immunol Lett* 1999; **68:** 125–34.

7 Middelhoven PJ, Ager A, Roos D, Verhoeven AJ. Involvement of a metalloprotease in the shedding of human neutrophil FcγRIII. *FEBS Lett* 1997; **414:** 14–18.

8 Gallea-Robache S, Morand V, Millet S, Bruneau JM, Bhatnagar N, Chouaib S *et al.* A metalloproteinase inhibitor blocks the shedding of soluble cytokine receptors and processing of transmembrane cytokine precursors in human monocytic cells. *Cytokine* 1997; **9:** 340–6.

9 Galon J, Moldovan I, Galinha A, Provost-Marloie MA, Kaudewitz H, Roman-Roman S *et al.* Identification of the cleavage site involved in production of plasma soluble Fc gamma receptor type III (CD16). *Eur J Immunol* 1998; **28:** 2101–7.

10 Middelhoven PJ, van Buul JD, Kleijer M, Roos D, Hordijk PL.

Actin polymerization induces shedding of FcgammaRIIIb (CD16) from human neutrophils. *Biochem Biophys Res Commun* 1999; **255:** 568–74.

11 Salmon JE, Edberg JC, Brogle NL, Kimberly RP. Allelic polymorphisms of human Fcgamma receptor IIA and Fcgamma receptor IIIB. Independent mechanisms for differences in human phagocyte function. *J Clin Invest* 1992; **89:** 1274–81.

12 Bone RC. Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). *JAMA* 1992; **268:** 3452–5.

13 Jost CR, Huizinga TWJ, de Goede R, Fransen JA, Tetteroo PA, Daha MR *et al.* Intracellular localization and *de novo* synthesis of FcRIII in human neutrophil granulocytes. *Blood* 1990; **75:** 144–51.

14 Guyre PM, Campbell AS, Kniffin WD, Fanger MW. Monocytes and polymorphonuclear neutrophils of patients with streptococcal pharyngitis express increased numbers of type I IgG Fc receptors. *J Clin Invest* 1990; **86:** 1892–6.

15 Petroni K, Shen L, Guyre PM. Modulation of human polymorphonuclear leukocyte IgG Fc receptors and Fc receptor-mediated functions by IFN-γ and glucocorticoids. *J Immunol* 1988; **140:** 3467–72.

16 Ierino FL, Powell MS, McKenzie IFC, Hogarth PM. Functional recombinant soluble human Fc gammaRII. *Transplant Proc* 1992; **24:** 2326–7.

17 Salmon JE, Brogle NL, Edberg JC, Kimberly RP. Fcγ receptor III induces actin polymerization in human neutrophils and primes phagocytosis mediated by Fcγ receptor II. *J Immunol* 1991, **146:** 997–1004.

18 Low MG. Biochemistry of the glycosyl-phosphatidylinositol membrane protein anchors. *Biochem J* 1987; **244:** 1–13.

19 Huizinga TWJ, de Haas M, Kleijer M, Nuijens JH, von Roos D, dem Borne AEG. Soluble Fcgamma receptor III in human plasma originates from release by neutrophils. *J Clin Invest* 1990; **86:** 416–23.

20 Utoh J, Yamamoto T, Utsonimia T, Kambara T, Goto H, Miyauchi Y. Effect of surgery on neutrophil functions, superoxide and leukotriene production. *Br J Surg* 1988; **75:** 682–5.

21 Carey PD, Wakefield CH, Thayeb A, Monson JRT, Guillou PJ. Preservation of neutrophil antimicrobial function after laparoscopic surgery. *Br J Surg* 1992; **79:** 1223 (Abstract).

Original article

Risk modelling study for carotid endarterectomy

G. Kuhan, E. D. Gardiner*, A. F. Abidia, I. C. Chetter, P. M. Renwick, B. F. Johnson, A. R. Wilkinson and P. T. McCollum

Academic Vascular Unit, Hull Royal Infirmary and *Applied Statistics Centre, University of Hull, Hull, UK
Correspondence to: Professor P. T. McCollum, Academic Vascular Unit, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK
(e-mail: peter.mccollum@virgin.net)

Background: The aims of this study were to identify factors that influence the risk of stroke or death following carotid endarterectomy (CEA) and to develop a model to aid in comparative audit of vascular surgeons and units.

Methods: A series of 839 CEAs performed by four vascular surgeons between 1992 and 1999 was analysed. Multiple logistic regression analysis was used to model the effect of 15 possible risk factors on the 30-day risk of stroke or death. Outcome was compared for four surgeons and two units after adjustment for the significant risk factors.

Results: The overall 30-day stroke or death rate was 3·9 per cent (29 of 741). Heart disease, diabetes and stroke were significant risk factors. The 30-day predicted stroke or death rates increased with increasing risk scores. The observed 30-day stroke or death rate was 3·9 per cent for both vascular units and varied from 3·0 to 4·2 per cent for the four vascular surgeons. Differences in the outcomes between the surgeons and vascular units did not reach statistical significance after risk adjustment.

Conclusion: Diabetes, heart disease and stroke are significant risk factors for stroke or death following CEA. The risk score model identified patients at higher risk and aided in comparative audit.

Paper accepted 16 August 2001

British Journal of Surgery 2001, **88**, 1590–1594

Introduction

Stroke is the third most common cause of death in the industrialized world. The benefit of carotid endarterectomy (CEA) in the prevention of stroke in patients with a symptomatic high-grade internal carotid artery stenosis (70–99 per cent) has been proven by randomized controlled trials[1–3]. For CEA to be worthwhile, the long-term benefit (stroke prevention) must outweigh the immediate operative risk (stroke and death). Current opinion suggests that most symptomatic patients will benefit from CEA if the combined 30-day stroke or death rate is less than 6 per cent[4]. Since the emergence of clinical governance there has been a strong emphasis on the comparative audit of outcome. Crude mortality and morbidity rates have been used widely to compare surgical outcome, but adjustment by case-mix is necessary if meaningful comparisons are to be made[5].

The published 30-day risk of stroke or death after CEA varies from 2 to 20 per cent[6]. The reasons for this wide variation in outcome are not immediately obvious. Risk modelling may identify the causes, and may be used to set clinical standards for vascular surgeons and units. Risk modelling using mathematical techniques has been used in cardiology and cardiac surgery[7,8]. The aims of this study were to identify the risk factors that influenced outcome following CEA and to develop a model that accurately predicted outcome to aid in comparative audit.

Patients and methods

A series of 839 CEAs performed by four vascular surgeons from two vascular units (A and B) for the interval 1992–1999 was available for analysis. Unit B had entirely prospective data (41·3 per cent of the data) while unit A had prospective and retrospective data (58·7 per cent). During the study one surgeon (surgeon 4) moved from unit B to A and performed 31 CEAs (7·1 per cent of CEAs performed in unit A). The data were collected on preprinted sheets and later entered into a vascular database based on Access 97 (Microsoft Corporation, Redmond, Washington, USA).

The median age of the patients was 68 (range 38–86) years and 60·4 per cent were men. Data on 67 possible

---

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Selected risk factors for the model

Age
Sex
Hypertension
Heart disease
Diabetes
Stroke
Renal failure
Contralateral internal carotid artery occlusion
Respiratory disease
Side of operation
Shunt
Patch
ASA grade
Surgeon
Vascular unit

ASA, American Society of Anesthesiologists

risk factors were collected (46 preoperative, 21 operative). Based on previously published series and univariate analysis, 15 risk factors were selected for analysis in order to simplify the dataset (*Table 1*). In this study diabetic patients (insulin and non-insulin dependent) were combined with patients who had impaired glucose tolerance and compared with normoglycaemic patients. Patients with angina, previous myocardial infarction, heart failure and cardiac arrhythmia were grouped into a single variable designated 'heart disease'. Patients who had only electrocardiographic evidence of ischaemic heart disease were analysed separately. Patients who presented with a stroke were compared with patients who had amaurosis fugax, transient ischaemic attack (TIA) and asymptomatic carotid disease. Non-hemispheric symptoms and vertebrobasilar symptoms were categorized as asymptomatic with respect to carotid disease. Patients who had a preoperative diagnosis of hypertension were compared with normotensive patients. Preoperative systolic blood pressure was analysed as a separate variable. The respiratory history was used to classify patients into those with normal, mild, moderate and severe respiratory disease. The results of chest radiography were analysed separately. The outcome endpoints used in the study were the occurrence of major stroke or death within 30 days of the operation. Major stroke was defined as a neurological deficit lasting more than 7 days. Outcome events were identified by the relevant surgical team for the prospective data while case-note review was relied upon for the retrospective data. All procedures were performed under general anaesthesia and systemic heparinization was routine before internal carotid artery clamping.

Logistic regression analysis was used on Statistical Package for the Social Sciences version 9.0 for Windows (SPSS, Chicago, Illinois, USA) to model the risk factors on the 30-day risk of stroke or death. The backward elimination method was used with a significance level set at 0·10 for model selection. The selected risk factor model was simplified further to produce a composite risk score model. A risk score was assigned to each risk factor depending on its parameter estimate.

Table 2 Significant risk factors identified by logistic regression analysis

Risk factor	Parameter estimate	Standard error	*P*
Heart disease	0·992	0·402	0·014
Diabetes	0·996	0·450	0·027
Stroke	0·827	0·394	0·036

The parameter estimates can be interpreted in terms of odds ratios. For example, the odds ratio for occurrence of a serious event for a patient presenting with heart disease relative to a patient without heart disease, but an otherwise identical pattern of risk factors, is given by the inverse natural logarithm of 0·992 which equals 2·70

A commonly encountered problem with any automated model selection process is overfitting the model to the analysed data set[9]. To overcome overfitting, shrinkage adjustment was performed using a shrinkage factor[10]. Shrinkage adjustment produces a model that is more suitable for future data and less specific for data used to develop the model. The final model produced was then used to compare surgeons and units by adding the factors pertaining to the surgeons and the units separately to the selected model.

Results

Ninety-eight CEAs were excluded owing to missing data on one or more of the possible risk factors analysed in the regression model. The stroke or death rate was 4·1 per cent (four of 98) in the excluded sample and was not statistically different from that of the sample analysed in terms of patient demographic factors or risk factors. Of the remaining 741 CEAs, 450 (60·7 per cent) were performed using an intraoperative shunt and 448 (60·5 per cent) were repaired with a patch. The indications for surgery were previous stroke (33·3 per cent), TIA (37·7 per cent), amaurosis fugax (16·2 per cent) and asymptomatic disease (12·8 per cent).

The overall 30-day stroke or death rate was 3·9 per cent (29 of 741). The observed mortality rate was 2·0 per cent (15 of 741). The causes of death were stroke (nine patients), myocardial infarction (five) and heart failure (one).

Regression modelling identified heart disease, diabetes and stroke as significant risk factors (*Table 2*). The parameter estimates were similar for all three risk factors. To obtain an easily interpretable model a risk score of 1 was assigned to each of these risk factors to produce a risk score model. A statistical comparison of the risk factor model and risk score model demonstrated that the simpler risk score model fitted the data just as well as the risk factor model (log likelihood ratio χ^2 test value = 0·089, 2 d.f., P = 0·814). The rate of stroke or death with respect to significant risk factors is given in *Table 3*; for example, the presence of diabetes carried an operative risk of 9·8 per cent compared with 3·2 per cent in non-diabetic patients.

The shrinkage factor was found to be 0·917. After multiplication of the estimated risk score regression coefficient by the shrinkage factor, the regression equation was as follows:

$$\text{Ln}\,(P/(1 - P)) = -4{\cdot}2726 + 0{\cdot}8524\ (\text{risk score})$$

where Ln = natural logarithm, P = probability of occurrence of the 30-day event, −4·2726 = intercept estimate, 0·8524 = coefficient estimate. The P value for the risk score coefficient estimate after adjustment for shrinkage was 0·022.

The predicted 30-day stroke or death rates after shrinkage adjustment for each possible risk score are shown in *Table 4*. The 30-day stroke or death rate associated with a risk score of 0 (no significant risk factors) was low (1·4 per cent), rising to 15·3 per cent for a risk score of 3 (presence of all three risk factors).

The observed 30-day stroke or death rates for four vascular surgeons studied were 4·2, 4·0, 3·0 and 3·9 per cent. The total number of CEAs performed by each surgeon and the percentage of high-, medium- and low-risk patients are shown in *Table 5*. The differences in outcome between the surgeons were not statistically significant after allowing for risk adjustment using the model (P = 0·977).

Vascular units A and B had an identical observed 30-day stroke or death rate of 3·9 per cent (*Table 6*). However, unit

Table 3 Rates of of stroke or death after carotid endarterectomy for each significant risk factor

	30-day stroke or death	
Risk factor	No	Yes
Heart disease		
No	415	10 (2·4)
Yes	297	19 (6·0)
Diabetes		
No	638	21 (3·2)
Yes	74	8 (9·8)
Stroke		
No	481	13 (2·6)
Yes	231	16 (6·5)

Values in parentheses are percentages

Table 4 Observed and predicted 30-day stroke or death rate for risk scores after shrinkage

Risk score	Observed 30-day stroke or death risk (%)	Predicted 30-day stroke or death risk (%)	Confidence interval (%)
0	1·6	1·4	0·9–2·1
1	3·1	3·2	2·1–4·8
2	8·9	7·2	2·5–19·0
3	18·1	15·3	2·8–53·1

Table 6 Comparative audit of two vascular units

	Unit A	Unit B
No. of operations	435	306
Stroke or death rate (%)	3·9	3·9
High risk (%)*	16·5	20·6
Medium risk (%)*	43·4	53·6
Low risk (%)*	40·0	25·8
Parameter estimate	0·155	0
Standard error	0·395	—
P	0·695	—

The default Statistical Package for the Social Sciences parameterization has been used so that the given parameter estimates for unit A represent comparison with unit B. Thus, the estimate of 0·155 for unit A implies that for two patients with identical patterns of risk factors the logarithm of the odds of a serious event occurring for unit A is 0·155 more than that for unit B. *A risk score of 2 or 3 was categorized as high risk, a risk score of 1 was categorized as medium risk and a risk score of 0 was categorized as low risk

Table 5 Comparative audit of vascular surgeons

	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4
No. of operations	215	101	88	337
Stroke or death rate (%)	4·2	4·0	3·0	3·9
High risk (%)*	17·7	18·8	10·0	20·5
Medium risk (%)*	41·9	42·6	48·0	52·8
Low risk (%)*	40·4	38·6	42·0	26·7
Parameter estimate	0·168	0·149	0·217	0
Standard error	0·454	0·598	0·666	—
P	0·711	0·804	0·745	—

The default Statistical Package for the Social Sciences parameterization has been used so that the given parameter estimates for surgeons 1, 2 and 3 represent comparison with surgeon 4. Thus, the estimate of 0·168 for surgeon 1 implies that for two patients with identical patterns of risk factors the logarithm of the odds of a serious event occurring for surgeon 1 is 0·168 more than that for surgeon 4. *A risk score of 2 or 3 was categorized as high risk, a risk score of 1 was categorized as medium risk and a risk score of 0 was categorized as low risk. P = 0·977 for removal of surgeon factor (Wald test)

B had a higher percentage of high-risk patients (20·6 per cent) than unit A (16·5 per cent). Nevertheless, after allowing for risk adjustment using this model, the differences between the two vascular units were not statistically significant ($P = 0{\cdot}695$).

Discussion

The 30-day stroke or death rate and the 30-day mortality rate obtained in this study were low compared with those of the large randomized controlled trials[1–3]. Similar event rates, however, have been obtained in other large series reported in the literature[6]. This study identified diabetes, heart disease and stroke at presentation as significant risk factors for 30-day stroke or death following CEA. These three risk factors had an additive effect on the operative risk. Diabetes is a well known risk factor for stroke and myocardial infarction[11]. In the North American Symptomatic Carotid Endarterectomy Trial diabetes was associated with a twofold increase in the risk of perioperative stroke or death[12]. Following a stroke, diabetics have a fourfold increased risk of early death compared with non-diabetics. Diabetic patients might be more prone to extensive infarction and cerebral oedema than non-diabetics[13].

Pre-existing heart disease is associated with an increased operative risk of stroke or death. A retrospective study of 1160 CEAs performed over 3 years demonstrated that the presence of angina before operation resulted in a significant increase in operative risk[14]. A similar study on 291 patients identified angina and congestive heart failure as significant risk factors for CEA[15]. However, in the presence of atrial fibrillation the risk of stroke can increase up to sevenfold[11].

Preoperative stroke is associated with a high perioperative stroke risk[16,17]. A study of 3062 CEAs performed over 26 years identified preoperative stroke as one of the significant risk factors for perioperative stroke on multivariate analysis[18]. The 30-day mortality rate after a stroke is 8–20 per cent. Diabetes, hypertension and heart disease have been shown to increase the rate of stroke recurrence[19,20]. These studies suggest that diabetes, stroke and heart disease are significant risk factors for death and morbidity in both surgical and non-surgical patients.

The modelling technique developed in this study could be adapted by other surgical units. The risk score logistic regression model has the advantages of simplicity and clinical interpretability. The parameter estimates in a logistic regression model can be interpreted easily using odds ratios (*Table 2*). In contrast, the weighting assigned to risk factors in non-linear statistical models (artificial neural networks and Bayesian analysis) cannot be interpreted simply[21].

A large sample size is needed to model risk factors influencing binary outcomes when the overall event rate is as low as 3–4 per cent. Data collected prospectively from unit B were combined with mixed prospective and retrospective data from unit A to achieve sufficient numbers to produce a reasonable model. The full data set was used to develop the model. Splitting the data set into a training set and a validation set would have left fewer outcome events per risk variable analysed[22]. Instead, the estimated risk score regression coefficient was multiplied by a shrinkage factor. The factor was estimated using a simple estimator known as the heuristic estimator[10]. The numerical effect of the multiplication was to bring closer together the predicted 30-day stroke or death rates for any two different risk scores. Thus this method anticipates and adjusts for the poorer discriminatory power of the developed risk score model on new data. There is no evidence that widely used computer intensive methods such as bootstrapping and cross-validation to estimate shrinkage factors provide significant advantages over the heuristic estimator[23]. Initially 67 variables were collected but only 15 were entered into the regression model. Entering all 67 variables into the selection process in a low-outcome event rate study would have rendered the model unreliable[9]. The 67 variables were reduced to 15 using previous studies and univariate analysis.

The confidence intervals given in *Table 4* after shrinkage indicate that the risk of 30-day stroke or death was acceptable for patients with a risk score of 0 or 1. For risk scores of 2 or 3 the confidence intervals were much wider and the interpretation less clear. The wide confidence intervals reflect the infrequent occurrence of stroke or death following CEA in this study. Successful identification inevitably questions the benefit of surgery in high-risk patients. These patients are also at a higher risk of stroke on best medical treatment alone. At present it is unclear which of these high-risk patients will benefit from CEA. A risk model developed using the European Carotid Surgery Trialists' Collaborative Group data attempted to identify patients who are at high risk on medical treatment but are at low risk at surgery; these should benefit the most from CEA[24]. The same study highlighted the need for external validation of risk models. The current risk score model also needs further validation on independent data sets.

Risk modelling techniques will become critical components in the delivery of targets set by the National Health Service Executive[25]. Comparison of crude outcome rates is often misleading. This study has demonstrated that risk models can be used to stratify patients into subgroups that will add validity to the outcome analysis. Differences in outcome between surgeons and units identified by risk modelling should encourage changes in clinical practice to improve the standard of care. Risk models may also be used to address the need for centralization of specialist vascular services[26,27].

Acknowledgements

This study was funded by a fellowship grant from the Royal College of Surgeons of England.

References

1 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. *N Engl J Med* 1991; **325:** 445–53.

2 European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991; **337:** 1235–43.

3 Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA *et al.* for the Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA* 1991; **266:** 3289–94.

4 Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott T *et al.* Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the Ad Hoc Committee, American Heart Association. *Stroke* 1995; **26:** 188–201.

5 Rothwell PM, Warlow CP. Interpretation of operative risks of individual surgeons. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1999; **353:** 1325.

6 Rothwell PM, Slattery J, Warlow CP. A systematic comparison of the risks of stroke and death due to carotid endarterectomy for symptomatic and asymptomatic stenosis. *Stroke* 1996; **27:** 266–9.

7 Edwards FH, Albus RA, Zajtchuk R, Graeber GM, Barry M. A quality assurance model of operative mortality in coronary artery surgery. *Ann Thorac Surg* 1989; **47:** 646–9.

8 Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. *Ann Thorac Surg* 2000; **69:** 823–8.

9 Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15:** 361–87.

10 Van Houwelingen JC, Le Cressie S. Predictive value of statistical models. *Stat Med* 1990; **9:** 1303–25.

11 Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham study. *Stroke* 1991; **22:** 312–18.

12 Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. The North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998; **339:** 1415–25.

13 Oppenheimer SM, Hoffbrand BI, Oswald GA, Yudkin JS. Diabetes mellitus and early mortality from stroke. *BMJ* 1985; **291:** 1014–15.

14 McCrory DC, Goldstein LB, Samsa GP, Oddone EZ, Landsman PB, Moore WS *et al.* Predicting complications of carotid endarterectomy. *Stroke* 1993; **24:** 1285–91.

15 Wong JH, Findlay J, Suarez-Almazor ME. Regional performance of carotid endarterectomy. Appropriateness, outcomes, and risk factors for complications. *Stroke* 1997; **28:** 891–8.

16 Rockman CB, Cappadona C, Riles TS, Lamparello PJ, Giangola G, Adelman MA *et al.* Causes of the increased stroke rate after carotid endarterectomy in patients with previous strokes. *Ann Vasc Surg* 1997; **11:** 28–34.

17 Takolander RJ, Bergentz SE, Ericsson BF. Carotid artery surgery in patients with minor stroke. *Br J Surg* 1983; **70:** 13–16.

18 Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA *et al.* The cause of perioperative stroke after carotid endarterectomy. *J Vasc Surg* 1994; **19:** 206–16.

19 Alter M, Sobel E, McCoy RL, Francis ME, Davanipour Z, Shofer F *et al.* Stroke in the Lehigh Valley: risk factors for recurrent stroke. *Neurology* 1987; **37:** 503–7.

20 Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. *Stroke* 1989; **20:** 983–9.

21 Schwarzer G, Vach W, Scumacher M. On the misuses of artificial neural networks for prognostic and diagnostic classification in oncology. *Stat Med* 2000; **19:** 541–61.

22 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49:** 1373–9.

23 Schumacher M, Hollander N, Sauerbrei W. Resampling and cross-validation techniques: a tool to reduce bias caused by model building? *Stat Med* 1997; **16:** 2813–27.

24 Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1999; **353:** 2105–10.

25 NHS Management Executive. *Clinical Governance: Quality in the New NHS.* London: Department of Health, 1999.

26 Cebul RD, Snow RJ, Pine R, Hertzer NR, Norris DG. Indications, outcomes, and provider volumes for carotid endarterectomy. *JAMA* 1998; **279:** 1282–7.

27 Kucey DS, Bowyer B, Iron K, Austin P, Anderson G, Tu JV. Determinants of outcome after carotid endarterectomy. *J Vasc Surg* 1998; **28:** 1051–8.

Short note

Diverticular disease of the colon in Accra, Ghana

B. N. Baako

Department of Surgery, University of Ghana Medical School,
PO Box 4236, Accra, Ghana
Correspondence to: Dr B. N. Baako, Department of Surgery,
University of Ghana Medical School, PO Box 4236, Accra, Ghana
(e-mail: harleyreed@ighmail.com)

Paper accepted 2 July 2001

Introduction

Diverticular disease is said to be rare in Africans because of the high-fibre diet they consume. Septic complications are the main presenting symptoms in Western countries and the major cause of morbidity and mortality from the disease[1]. This 3-year (1997–2000) prospective study in one of four general surgical units in the Korle Bu Teaching Hospital in Accra examined the incidence and presentation of the disease in the indigenous Ghanaian population adherent to a high-fibre diet.

Patients and methods

All patients with symptoms and signs of diverticular disease and whose diagnosis was confirmed by barium enema and/or colonoscopy were included in the study. Proctoscopy and sigmoidoscopy were performed to exclude anorectal lesions that might have a similar presentation.

Results

Thirty-seven patients of mean age 60 (median 61) years were seen over the interval. The lesions were mainly diffuse ($n = 20$), with 13 confined to the right colon and 4 to the left colon. Rectal bleeding was the most common symptom (*Table 1*). Fourteen of these patients needed blood transfusions and formed a quarter of all patients needing blood transfusion for rectal bleeding over the study period. Septic complications were rare and mild. Seven of the 37 patients needed surgical intervention: one for obstruction, one for fistula and five for massive recurrent rectal bleeding.

Table 1 Presentation of diverticular disease in 1997–2000

	No. of patients	No. requiring surgery
Rectal bleeding	23	5
Constipation and/or abdominal cramps	10	1
Diverticulitis	2	0
Fistula	2	1
Total	37	7

Discussion

A 3-year study in the 1970s of a similar patient group in this hospital reported only 16 cases of diverticular disease[2]. These 37 cases over the same time period give an estimated annual incidence of 48 cases, indicating an increased incidence. The mean age of 60 years is similar to the 63·9 years reported in the Massachusetts General Hospital study[1]. This suggests the ageing process as an aetiological factor. Post-mortem studies[3], and the fact that changes in colonic tensile strength manifested by increased amounts of collagen and elastin in the colonic wall is associated with the ageing prcoess[4], support this view.

The young population coupled with inadequate health-delivery facilities may explain the apparent rarity of the disease in the African. The hypothesis that lack of dietary fibre to give bulk to the stool leads to increased intracolonic pressure and exaggerated colonic segmentation promoting the mucosal herniation is not supported by the present study.

Sepsis is a rare finding in the African patient with diverticular disease. This contrasts with the Massachusetts General Hospital study[1], which reported a septic complication rate of 58 and 44 per cent in two consecutive decades. A high-fibre diet may tend to prevent sepsis by ensuring regular faecal flow, thereby reducing blockage at the neck of the diverticulum and preventing stasis, bacterial proliferation and sepsis. It is of note that the decrease in mortality rate from diverticulitis in wartime Britain (1939–1945) was accredited to the high-fibre diet occasioned by the war[5].

This study suggests that the rarity of diverticular disease in Africa is predominantly the result of short life expectancy. High-fibre diet reduces the incidence of sepsis. Diverticular disease is a significant cause of massive rectal bleeding needing transfusion in Africa.

References

1 Rodkey GV, Welch CE. Changing patterns in the surgical treatment of diverticular disease. *Ann Surg* 1984; **200:** 466–78.
2 Archampong EQ, Christian F, Badoe EA. Diverticular disease in an indigenous African community. *Ann R Coll Surg Engl* 1978; **60:** 464–70.
3 Parks TG. Post-mortem studies on the colon with special reference to diverticular disease. *Proc R Soc Med* 1968; **61:** 932–4.
4 Eastwood MA, Watters DAK, Smith AN. Diverticular disease: is it a motility disorder? *Clin Gastroenterol* 1982; **11:** 545–61.
5 Painter NS, Burkitt DP. Diverticular disease in the colon: a deficiency disease of Western civilization. *BMJ* 1971; **ii:** 450–4.

Original article

Plasma concentration of tissue inhibitor of matrix metalloproteinase 1 in patients with colorectal carcinoma

N. Yukawa*§, T. Yoshikawa*§, M. Akaike*, Y. Sugimasa*, S. Takemiya*, S. Yanoma†, Y. Noguchi‡ and Y. Takanashi§

*Department of Gastrointestinal Surgery and †Department of Immunology, Research Institute, Kanagawa Cancer Centre, ‡Department of Surgery, Yokohama Kowan Hospital and §First Department of Surgery, Yokohama City University, School of Medicine, Yokohama, Japan
Correspondence to: Dr N. Yukawa, Department of Gastrointestinal Surgery, 1-1-2 Nakao, Asahi-Ku, Yokohama 241-0815, Japan
(e-mail: nryukawa@mac.com)

Background: The expression of tissue inhibitor of matrix metalloproteinase (TIMP) 1 in tumour tissue from patients with colorectal carcinoma has been reported to be related to disease progression. However, the clinical significance of plasma TIMP-1 has not been fully elucidated.
Methods: The plasma level of TIMP-1 protein was determined by enzyme-linked immunosorbent assay in samples from 54 patients who underwent resection of the primary tumour.
Results: Plasma TIMP-1 levels were associated significantly with depth of invasion and metastasis to lymph nodes and liver. Circulating TIMP-1 levels were significantly higher in patients with serosal invasion, liver metastases and Dukes' stage C tumours. Using a cut-off value of 160 ng/ml, serosal invasion and Dukes' C stage could be predicted with an accuracy of 68·5 per cent. With a cut-off value of 170 ng/ml, metastasis to the lymph node and liver could be predicted with an accuracy of 66·7 and 70·4 per cent respectively. These values were greater than those for carcinoembryonic antigen and CA19-9.
Conclusion: These data suggest that the plasma concentration of TIMP-1 correlates with both invasion and metastasis in patients with colorectal carcinoma.

Paper accepted 31 July 2001

British Journal of Surgery 2001, **88**, 1596–1601

Introduction

The degradation of extracellular matrix components is essential for tumour cells to invade surrounding tissues and metastasize to distant organs. Matrix degradation depends on the activities of both matrix metalloproteinases (MMPs) and tissue inhibitors of these enzymes (TIMPs)[1,2]. TIMPs act as negative regulators of the degradation process[1], and their expression has been reported to parallel the expression of MMPs[3]. Among the known TIMPs, TIMP-1 has strong inhibitory effects on various types of MMP[4]. Moreover, several studies have demonstrated a different function for TIMP-1 as a growth-stimulating factor for normal and malignant cells[5].

Recently, the clinical significance of TIMP-1 in gastrointestinal cancer has been examined. Nomura *et al.*[6] reported enhanced TIMP-1 production and Mimori *et al.*[7] demonstrated a positive correlation between TIMP-1 messenger RNA (mRNA) concentration and tumour progression in patients with gastric carcinoma. In patients with colorectal carcinoma, Zeng *et al.*[8] indicated that there was a correlation between TIMP-1 mRNA level and advanced stage. Holten-Andersen and co-workers[9] documented that the level of TIMP-1 in the plasma of patients with advanced colorectal carcinoma was higher than that of healthy blood donors. More recently, it has been reported that plasma concentration of TIMP-1 appears to correlate with both serosal invasion and metastasis in gastric carcinoma[10].

Although TIMP-1 can be measured in the blood of patients with a variety of carcinomas[11,12], the clinical significance of circulating TIMP-1 concentration in patients with colorectal cancer has not been fully evaluated. Oberg *et al.*[13] examined serum levels of MMP-2, MMP-9, TIMP-1 and TIMP-2 in patients with colorectal carcinoma and found that they were of limited value for tumour staging and prognosis. They demonstrated no correlation between serum TIMP-1 level and tumour progression[13]. Recently, circulating TIMP-1 was shown to be produced and released

---

The Editors have satisfied themselves that all authors have contributed significantly to this publication

by megakaryocytes and platelets[14]. Production by these cells in the blood would affect serum levels, rather than plasma levels. Therefore, serum may not be suitable for the measurement of circulating TIMP-1 concentration. Paralleling the changes observed in tumour tissue, however, TIMP-1 concentration in the plasma may serve as a simple, non-invasive tool that is useful in assessing tumour progression. This study measured the concentration of TIMP-1 protein in plasma from patients with colorectal carcinoma.

Patients and methods

Peripheral blood was collected from 54 patients with colorectal carcinoma, who underwent surgical resection between June 1999 and January 2000. Of the 54 patients, radical surgery for cure was undertaken in 44 and palliative resection was performed in ten patients with metastases to the peritoneum, lungs or liver. The clinical details of the patients are summarized in *Table 1*.

All samples of plasma and serum were obtained before treatment. Clinical and pathological classifications of resected tumours were undertaken according to rules adopted by the Japanese Research Society for Cancer of the Colon and Rectum[15]. Metastases to the liver and lung were diagnosed by computed tomography (CT) and ultrasonography. Peritoneal metastasis was diagnosed clinically in most patients and confirmed by pathological examination in some cases.

Table 1 Patient characteristics

	No. of patients
Sex ratio (M : F)	31 : 23
Mean (range) age (years)	63·52 (20–83)
Macroscopic type*	
0	3
1	7
2	36
3	7
4	0
5	1
Histological type	
Well differentiated, tubular	21
Moderately differentiated	32
Poorly differentiated	1
Lymph node metastasis	
Negative	24
Positive	30
Peritoneal metastasis	
Negative	51
Positive	3
Liver metastasis	
Negative	44
Positive	10

*According to Japanese Research Society for Cancer of the Colon and Rectum[15]

Measurement of tissue inhibitor of matrix metalloproteinase 1

Plasma TIMP-1 concentration was measured with a commercially available, one-step, sandwich enzyme-linked immunosorbent assay kit (Fuji Chemical, Takaoka, Japan)[16]. For the assay, 5 µl of properly diluted sample or serially diluted human TIMP-1 (standard) and 75 µl of peroxidase-conjugated antihuman TIMP-1 antibody were added to the wells of a microtitre plate. After a 30-min incubation at 30°C, the wells were washed with 0·05 per cent Tween 20 (Sigma, St Louis, Missouri, USA) in phosphate-buffered saline. Bound complexes were then incubated with *o*-phenylenediamine containing hydrogen peroxide for 15 min at 30°C. The reaction was stopped by adding hydrosulphuric acid 1 mol/l, and absorbance at 492 nm was measured with a microtitre plate reader. The limit of quantification for the assay was 51 ng/ml and a linear response was observed from 51 to 2000 ng/ml, with a coefficient of variation of less than 5·0 per cent.

Measurement of carcinoembryonic antigen and CA19-9

Serum concentrations of carcinoembryonic antigen (CEA) and CA19-9 were determined using a commercially available enzyme immunoassay kit (Dainabott, Tokyo, Japan) and an immunoradiometric assay kit (Centocor, Malvern, Pennsylvania, USA) respectively. The upper limits of normal as stated by the manufacturer were 2·5 ng/ml for CEA and 37·0 units/ml for CA19-9.

Statistical analysis

For comparisons between two groups, non-parametric analyses for paired and unpaired data and the χ^2 test were used. For more than three groups, one-way analysis of variance and Duncan's multiple range test were used. Correlations were evaluated with Spearman's rank correlation test (r). $P < 0{\cdot}05$ was considered statistically significant, and data were expressed as mean(s.d.).

Results

In patients with colorectal cancer, higher plasma TIMP-1 concentrations were associated with a variety of pathological factors, including depth of tumour invasion into the colorectal wall and metastasis to the lymph nodes and liver

Table 2 Plasma levels of tissue inhibitor of matrix metalloproteinase 1 in patients with colorectal carcinoma

	No. of patients	TIMP-1 (ng/ml)	P^*
Macroscopic type			n.s.
0	3	128·7(53·1)	
1	7	171·7(56·2)	
2	36	167·7(100·5)	
3	7	226·6(131·0)	
5	1	121·9	
Histological type			n.s.
Well differentiated, tubular	21	152·2(56·2)	
Moderately differentiated	32	183·7(117·4)	
Poorly differentiated	1	258·3	
Depth of invasion			< 0·05
Submucosa	4	126·6(43·6)	
Muscularis propria	5	124·6(29·8)	
Subserosa	7	150·8(52·0)	
Serosa exposed	27	159·6(49·7)	
Serosa invading	11	258·3(176·7)†	
Lymph node metastasis			< 0·05
N_0	24	146·7(39·6)	
N_1	14	168·6(49·8)	
N_2	9	164·9(62·9)	
N_3	6	299·4(243·7)‡	
N_4	1	173·0	
Peritoneal dissemination			n.s.
Absent	51	171·7(99·9)	
Present	3	192·0(72·2)	
Liver metastasis			< 0·05
Absent	44	162·8(94·9)	
Present	10	217·0(105·1)	
Lymphatic invasion			n.s.
Absent	33	155·8(51·2)	
Present	21		
Venous invasion			n.s.
Absent	11	141·0(36·0)	
Present	43		
Infiltration of tumour			n.s.
α	5	129·4(36·4)	
β	47	175·1(102·9)	
γ	2	229·3(41·0)	
Dukes' stage			n.s.
A	8	132·7(28·1)	
B	14	149·6(44·5)	
C	32	193·1(119·9)	

Values are mean(s.d.). Pathological measures according to the Japanese Research Society for Cancer of the Colon and Rectum[15]; α, infiltrative growth; β, expansive growth; γ, intermediate growth. TIMP-1, tissue inhibitor of matrix metalloproteinase 1; n.s., not significant among the group. *non-parametric tests; †$P < 0·05$ *versus* submucosa, muscularis propria, subserosa and serosa exposed (Duncan's multiple range test); ‡$P < 0·05$ *versus* N_0, N_1 and N_2 (Duncan's multiple range test)

Table 3 Concentration of circulating levels of tissue inhibitor of matrix metalloproteinase 1, carcinoembryonic antigen and CA19-9 in patients grouped according to clinicopathological factors

	No. of patients	TIMP-1 (ng/ml)	CEA (ng/ml)	CA19-9 (units/ml)
Serosal invasion				
Absent	14	134·5(45·6)	3·4(4·6)	19·2(12·5)
Present	38	188·1(110·6)	49·0(255·3)	188·9(616·6)
P^*		0·011	0·011	0·137
Lymph node metastasis				
Absent	22	146·3(41·2)	5·4(7·5)	31·2(25·2)
Present	30	193·8(123·8)	59·7(287·3)	225·4(691·6)
P^*		0·082	0·301	0·399
Liver metastasis				
Absent	42	163·4(97·1)	5·6(8·6)	112·5(483·3)
Present	10	217·0(105·1)	167·5(496·4)	272·5(713·4)
P^*		0·025	0·018	0·190
Dukes' stage				
A and B	20	142·7(41·1)	3·9(4·1)	31·9(25·8)
C	32	193·1(119·9)	57·3(278·1)	212·8(670·8)
P^*		0·036	0·079	0·535

Values are mean(s.d.). TIMP-1, tissue inhibitor of matrix metalloproteinase 1; CEA, carcinoembryonic antigen. *non-parametric tests

(*Table 2*). The concentration of TIMP-1 was significantly higher when tumours invaded the adjacent structures (serosal invasion), compared with tumours without invasion. Patients with metastases to level 3 lymph nodes had significantly higher levels of circulating TIMP-1 than those with metastases up to level 2 nodes. The concentration of circulating TIMP-1 was significantly higher in patients with liver metastasis than in those without.

The concentrations of circulating TIMP-1, CEA and CA19-9 were stratified according to pathological factors (*Table 3*). The plasma concentration of TIMP-1 was significantly higher in patients with serosal invasion, liver metastasis and Dukes' C stage tumours (*Fig. 1* and *Table 3*). However, circulating CEA level was related only to serosal invasion and liver metastasis. CA19-9 was not related to these factors at all. Patients with lymph node metastasis had slightly higher levels of TIMP-1 than those without, although the difference was not significant (*Table 3*). In these patients the correlation between TIMP-1 and CEA or CA19-9 concentration was not statistically significant ($r = 0·017, P = 0·905$ and $r = 0·119, P = 0·401$ respectively).

To examine further the predictive value of plasma TIMP-1 levels, the cut-off values for lymph node metastasis, serosal invasion and Dukes' classification were calculated based on the receiver–operater characteristics (*Table 4*). The predictive probability was then determined. Serosal invasion, lymph node metastasis, liver metastasis and Dukes' C stage could be predicted with an accuracy of 68·5, 66·7, 70·4 and 68·5 per cent respectively (*Table 4*). These values were greater than those for CEA and CA19-9.

Discussion

In patients with colorectal carcinoma, treatment strategy should depend on the factors that influence prognosis, such

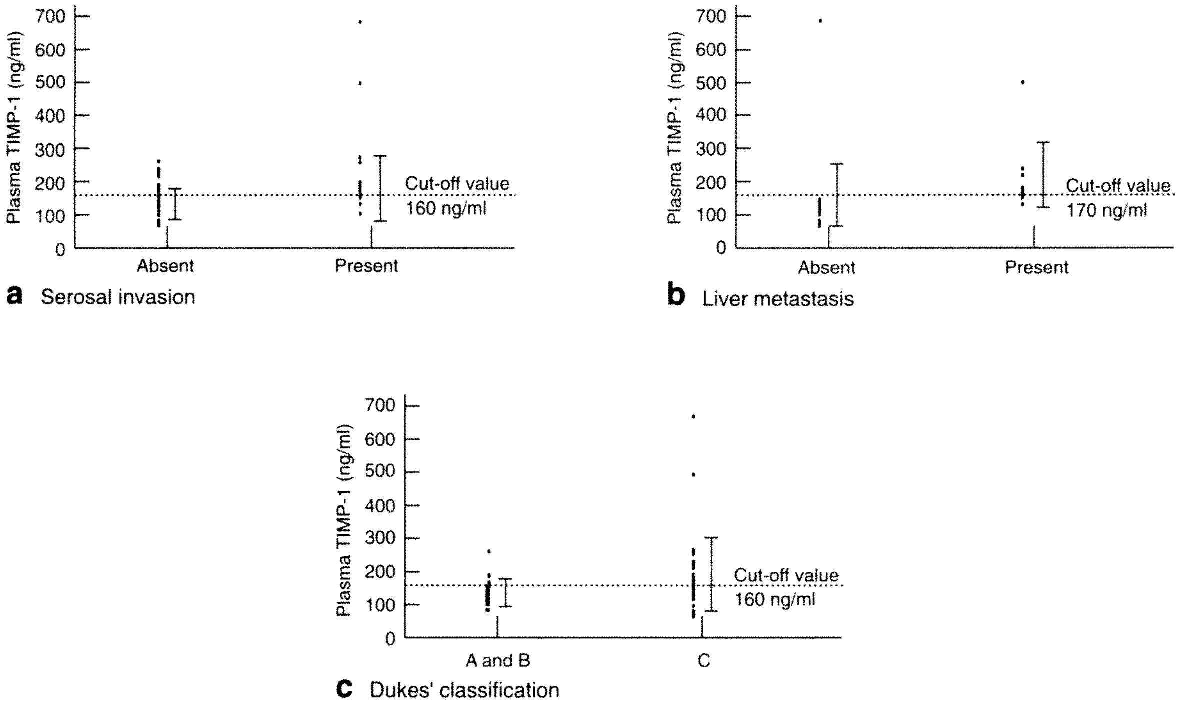


Fig. 1 Plasma tissue inhibitor of matrix metalloproteinase (TIMP) 1 concentrations and **a** serosal invasion, **b** liver metastasis and **c** Dukes' classification. Individual values are shown as well as the range of mean(s.d.) and cut-off values

Table 4 Cut-off values and predictive probability for serosal invasion, lymph node metastasis, liver metastasis and Dukes' classification

		Predictive probability (%)			
	Cut-off value	Sensitivity	Specificity	Accuracy	*P**
Serosal invasion					
CEA	2·7 ng/ml	82·8	41·7	64·2	0·049
CA19-9	37·0 units/ml	100·0	41·2	61·5	0·002
TIMP-1	160·0 ng/ml	92·0	48·3	68·5	0·001
Lymph node metastasis					
CEA	2·7 ng/ml	58·6	45·8	52·8	0·745
CA19-9	37·0 units/ml	66·7	47·1	53·8	0·341
TIMP-1	170·0 ng/ml	80·0	58·8	66·7	0·006
Liver metastasis					
CEA	2·7 ng/ml	27·6	91·7	56·6	0·075
CA19-9	37·0 units/ml	33·3	88·2	69·2	0·061
TIMP-1	170·0 ng/ml	35·0	91·2	70·4	0·017
Dukes' stage C					
CEA	2·7 ng/ml	65·5	45·8	56·6	0·400
CA19-9	37·0 units/ml	72·2	44·1	53·8	0·249
TIMP-1	160·0 ng/ml	80·0	58·6	68·5	0·004

Values are mean(s.d.). TIMP-1, tissue inhibitor of matrix metalloproteinase 1; CEA, carcinoembryonic antigen. $^*\chi^2$ test

as the extent of colorectal wall invasion, the extent of lymph node metastasis and the presence of distant metastases. If the preoperative determination of these factors were feasible, treatment could be customized to suit each patient. However, the tools currently available are not sufficiently sensitive to meet this need. CT and magnetic resonance imaging only provide information about apparent invasion to the adjacent organs and metastases to lymph nodes or liver. Microscopic and molecular analyses of tissue specimens may provide information about the aggressiveness of the tumour[17,18], but diagnosis based on a small piece of tissue may not be appropriate for the entire tumour. Moreover, there are problems with the reproducibility of molecular diagnoses. If an invasion- or metastasis-specific protein could be detected in peripheral blood, treatment strategy could be focused more specifically. Although CEA and CA19-9 have been used as tumour markers, increased levels of these antigens in peripheral blood have most often been associated with irresectable disease[19–21].

Recent advances in the understanding of the molecular mechanisms of invasion and metastasis have revealed significant direct roles for the various MMPs, including MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9, and membrane type (MT)-MMP-1 and MT-MMP-2[2,3,22–25]. These proteinases are produced by tumour cells or stromal cells, or both. Which MMP plays the dominant role in invasion depends on the tumour type. Once MMPs have been activated, specific TIMPs are induced in stromal cells to control proteinase reactions[24]. TIMP-1 has powerful inhibitory effects on various MMPs[4]. Recently, an association between TIMP-1 expression and disease progression was suggested in patients with colorectal carcinoma[26]. Moreover, in patients with colorectal cancer and distant metastases, plasma TIMP-1 levels were found to be significantly higher than those in healthy blood donors[9]. The present study clearly demonstrates that plasma concentrations of TIMP-1 are associated with tumour progression as measured by serosal invasion, lymph node metastasis, liver metastasis and Dukes' classification.

It is important to anticipate the depth of invasion, lymph node metastasis and Dukes' stage either before or during operation. Some early-stage colorectal carcinomas can be treated by limited surgery, including endoscopic resection and laparoscopic surgery. Thus, a preoperative diagnosis of lymph node metastasis and serosal invasion is necessary to anticipate whether minimal-access surgery is appropriate. Tumours without lymph node metastases could be treated by means of local resection. For tumours with serosal invasion, lymph node metastasis or Dukes' C stage, several investigators have suggested that laparoscopic surgery may be inappropriate because of the risk of port-site metastasis[27–29]. These minimal-access procedures may be contraindicated in patients with raised circulating levels of TIMP-1.

TIMP-1 was more accurate than other tumour markers in predicting serosal invasion, lymph node metastasis, liver metastasis and Dukes' staging. Moreover, no correlations between TIMP-1 and other markers were observed in the present study, suggesting that TIMP-1 may be an independent tumour marker for invasion and metastasis in patients with colorectal carcinoma.

In the absence of symptoms due to the tumour, surgical resection may not be recommended primarily for patients with advanced disease[30]. Such patients would be treated with chemotherapy or radiation therapy before operation[31]. Diagnosis of the metastases by imaging techniques such as CT has been useful, but imperfect. As shown in this study, TIMP-1 could be a marker for predicting those tumours. Although the predictive efficiency was not high, plasma TIMP-1 concentration may have value in determining the appropriate treatment strategy for patients with colorectal carcinoma before operation.

References

1 Tsuchiya Y, Sato H, Endo Y, Okada Y, Mai M, Sasaki T *et al.* Tissue inhibitor of metalloproteinase 1 is a negative regulator of the metastatic ability of a human gastric cancer cell line, KKLS, in the chick embryo. *Cancer Res* 1993; **53:** 1397–402.

2 Crawford HC, Matrisian LM. Tumor and stromal expression of matrix metalloproteinases and their role in tumor progression. *Invasion Metastasis* 1995; **14:** 234–45.

3 Urbanski SJ, Edwards DR, Hershfield N, Hucheroft SA, Shaffer E, Sutherland L *et al.* Expression pattern of metalloproteinases and their inhibitors changes with the progression of human sporadic colorectal neoplasia. *Diagn Mol Pathol* 1993; **2:** 81–9.

4 Denhardt TD, Feng B, Edwards DR, Cocuzzi ET, Malyankar UM. Tissue inhibitor of metalloproteinase (TIMP, aka EPA): structure, control of expression and biological functions. *Pharmacol Ther* 1993; **59:** 329–41.

5 Hayakawa T, Yamashita K, Tanzawa K, Uchijima E, Iwata K. Growth-promoting activity of tissue inhibitor of metalloproteinases-1 (TIMP-1) for a wide range of cells. A possible new growth factor in serum. *FEBS Lett* 1992; **298:** 29–32.

6 Nomura H, Fujimoto N, Seiki M, Mai M, Okada Y. Enhanced production of matrix metalloproteinases and activation of matrix metalloproteinase 2 (gelatinase A) in human gastric carcinomas. *Int J Cancer* 1996; **69:** 9–16.

7 Mimori K, Mori M, Shiraishi T, Fujie T, Baba K, Haraguchi M *et al.* Clinical significance of tissue inhibitor of metalloproteinase expression in gastric carcinoma. *Br J Cancer* 1997; **76:** 531–6.

8 Zeng ZS, Cohen AM, Zhang ZF, Stetler-Stevenson W, Guillem JG. Elevated tissue inhibitor of metalloproteinase 1 RNA in colorectal cancer stroma correlates with lymph node and distant metastases. *Clin Cancer Res* 1995; **1:** 899–906.

9 Holten-Andersen MN, Murphy G, Nielsen HJ, Pedersen AN, Christensen IJ, Hoyer-Hansen G *et al.* Quantitation of TIMP-1 in plasma of healthy blood donors and patients with advanced cancer. *Br J Cancer* 1999; **80:** 495–503.

10 Yoshikawa T, Saitoh M, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H *et al.* Tissue inhibitor of metalloproteinase-1 in the plasma of patients with gastric carcinoma. A possible

marker for serosal invasion and metastasis. *Cancer* 1999; **86:** 1929–35.

11 Baker T, Tickle S, Wasan H, Docherty A, Isenberg D, Waxman J. Serum metalloproteinases and their inhibitors: markers for malignant potential. *Br J Cancer* 1994; **70:** 506–12.

12 Jung K, Nowak L, Lein M, Priem F, Schnorr D, Loening SA. Matrix metalloproteinases 1 and 3, tissue inhibitor of metalloproteinase-1/tissue inhibitor in plasma of patients with prostate cancer. *Int J Cancer* 1997; **74:** 220–3.

13 Oberg A, Hoyhtya M, Tavelin B, Stenling R, Lindmark G. Limited value of preoperative serum analysis of matrix metalloproteinases (MMP-2, MMP-9) and tissue inhibitors of matrix metalloproteinases (TIMP-1, TIMP-2) in colorectal cancer. *Anticancer Res* 2000; **20:** 1085–91.

14 Murate T, Yamashita K, Isogai C, Suzuki H, Ichihara M, Hatano S *et al.* The production of tissue inhibitors of metalloproteinases (TIMPs) in megakaryopoiesis: possible role of platelet- and megakaryocyte-derived TIMPs in bone marrow fibrosis. *Br J Haematol* 1997; **99:** 181–9.

15 Japanese Research Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum, and Anus in Japan.* Tokyo. Kanehara, 1998.

16 Kodama S, Iwata K, Iwata H, Yamashita K, Hayakawa T. Rapid one-step sandwich enzyme immunoassay for tissue inhibitor of metalloproteinases. An application for rheumatoid arthritis serum and plasma. *J Immunol Methods* 1990; **127:** 103–8.

17 Segal AW, Healy MJ, Cox AG, Williams I, Slavin G, Smithers A *et al.* Diagnosis of gastric cancer. *BMJ* 1975; **2:** 669–72.

18 Tahara E, Semba S, Tahara H. Molecular biological observations in gastric cancer. *Semin Oncol* 1996; **23:** 307–15.

19 Horie Y, Miura K, Matsui K, Yukimasa A, Ohi S, Hamamoto T *et al.* Marked elevation of plasma carcinoembrionic antigen and stomach cancer. *Cancer* 1996; **77:** 1991–7.

20 Koga T, Kano T, Souda K, Oka N, Inokuchi K. The clinical usefulness of preoperative CEA determination in gastric cancer. *Jpn J Surg* 1987; **17:** 342–7.

21 Wobbes T, Thomas CMG, Segers MFG, Nagengast FM. Evaluation of seven tumor markers (CA50, CA19-9, TruQuant, CA72-4, CA195, carcinoembryonic antigen, and tissue polypeptide antigen) in the pretreatment sera of patients with gastric carcinoma. *Cancer* 1992; **69:** 2036–41.

22 Stetler-Stevenson WG, Liotta LA, Kleiner DE Jr. Extracellular matrix 6: role of matrix metalloproteinases in tumor invasion and metastasis. *FASEB J* 1993; **7:** 1434–41.

23 Takino T, Sato H, Yamamoto E, Seiki M. Cloning of a human gene potentially encoding a novel matrix metalloproteinase having a C-terminal transmembrane domain. *Gene* 1995; **155:** 293–8.

24 Sato H, Kida Y, Mai M, Endo Y, Sasaki T, Tanaka J *et al.* Expression of genes encoding type IV collagen-degrading metalloproteinases and tissue inhibitors of metalloproteinases in various human tumor cells. *Oncogene* 1992; **7:** 77–83.

25 Sato H, Takino T, Okada Y, Cao J, Shinagawa A, Yamamoto E *et al.* A matrix metalloproteinase expressed on the surface of invasive tumour cells. *Nature* 1994; **370:** 61–5.

26 Joo YE, Seo KS, Kim J, Kim HS, Rew JS, Park CS *et al.* Role of tissue inhibitors of metalloproteinase (TIMPs) in colorectal carcinoma. *J Korean Med Sci* 1999; **14:** 417–23.

27 Wexner SD, Cohen SM. Port site metastasis after laparoscopic colorectal surgery for cure of malignancy. *Br J Surg* 1995; **82:** 295–8.

28 Adachi Y, Sato K, Shiraishi N, Kakisako K, Tanimura H, Kitano S. Tumor size of colorectal cancer: indication for laparoscopic surgery. *Surg Laparosc Endosc* 1998; **8:** 269–72.

29 Boulez J, Espalieu P, Fontaumard E, Meeus P. Laparoscopic colo-rectal surgery: analysis of 113 cases. *Hepatogastroenterology* 1997; **44:** 40–4.

30 Chaudhry V, Nittala M, Prasad ML. Preoperative chemoradiation and coloanal J pouch reconstruction for low rectal cancer. *Am Surg* 2000; **66:** 387–93.

31 Guillem JG, Calle JP Jr, Akhurst T, Tickoo S, Ruo L, Minsky BD *et al.* Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. *Dis Colon Rectum* 2000; **43:** 18–24.

Original article

Salvage abdominal surgery in patients with a retained rectal stump after restorative proctocolectomy and stapled anastomosis

H. Tulchinsky, J. S. McCourtney, K. V. Subba Rao, W. Chambers, J. Williams, K. H. Wilkinson and R. J. Nicholls

St Mark's Hospital, Watford Road, Harrow HA1 3JU, UK
Correspondence to: Professor R. J. Nicholls (e-mail: john.nicholls@nwlh.nhs.uk)

Background: The introduction of surgical stapling instruments has widened the use of restorative proctocolectomy. Too high a distal transection of the rectum can, however, produce a retained rectal stump, which may cause symptoms. A study of the operative and functional data in a consecutive series of patients undergoing salvage surgery for retained rectal stump was undertaken.

Methods: Twenty-five patients referred between January 1990 and September 2000 for pouch dysfunction were identified as having a retained rectal stump. Twenty-two underwent abdominoanal revision. The hospital notes were reviewed and function was assessed during outpatient visits, by postal questionnaire and by telephone interview.

Results: Median operating time was 225 (range 170–340) min and median hospital stay was 15 (range 8–48) days. There was no operative death. Five pouches were excised. Seventeen patients were available for functional assessment. Median follow-up was 22·5 (range 4–114) months. Median 24-h frequency before and after operation was 12 (range 4–20) and 6 (range 3–12) respectively, and median night-time frequency was 4 (range 0–8) and 0·5 (range 0–4) respectively. Fifteen patients reported marked subjective improvement in pouch function and quality of life.

Conclusion: Major revisional surgery for symptomatic retained rectal stump after restorative proctocolectomy with stapled anastomosis was successful in 15 of 22 patients. These results are worse than the outcome following first-time restorative proctocolectomy with anastomosis constructed at the anal level. Pouch–rectal anastomosis should be avoided.

Paper accepted 31 July 2001

British Journal of Surgery 2001, **88**, 1602–1606

Introduction

Restorative proctocolectomy with ileal pouch–anal anastomosis has become the surgical treatment of choice for ulcerative colitis and for most patients with familial adenomatous polyposis[1–5]. The availability of stapling instruments has placed the operation into the repertoire of most surgeons with a colorectal interest. However, a stapled ileal pouch–anal anastomosis requires accurate transection at the anorectal junction to avoid leaving behind persisting disease. When this occurs in the patient with ulcerative colitis, inflammation in the rectal segment may cause local symptoms of bleeding, burning and urgency[2,3]. There may be disordered evacuation with the frequent passage of small amounts of stool, and such patients may still be at risk of developing cancer. The authors' experience with revisional surgery for patients referred with a symptomatic retained rectal stump after restorative proctocolectomy is described.

Patients and methods

All patients referred with ileal pouch dysfunction and subsequently found to have a retained rectal stump were identified. They were defined by the level of the anastomosis between the ileal reservoir and the distal bowel in relation to the anorectal junction, determined by clinical, endoscopic and contrast radiological evaluation[6,7]. Histopathological reports of the operative specimen were reviewed.

Between January 1990 and September 2000, 25 consecutive patients (12 women, 13 men) were identified.

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Preoperative diagnoses included colorectal cancer (one patient), familial adenomatous polyposis (one) and ulcerative colitis (23). One patient had metachronous cancer in the retained rectal stump and chose to return to his home country for further treatment. A second patient was treated by endoanal mucosectomy and endoanal pouch advancement, and a third patient with minimal symptoms of pouch dysfunction but perianal sepsis was treated by seton drainage and rejected for revisional surgery because of severe Parkinson's disease. The remaining 22 patients (11 women, 11 men; polyposis, one; colitis, 21) underwent combined abdominal and endoanal pouch revision.

The operative technique included certain principles. Close rectal dissection[8] was employed to minimize the chance of damage to the pelvic nerves. When necessary, a new pouch was formed or the existing pouch modified with an extra small-bowel loop using a hand-sewn technique. Endoanal mucosectomy after submucosal infiltration with saline and adrenaline (1 : 300 000 dilution) was performed routinely. The pouch–anal anastomosis was performed manually with endoanal exposure using an Eisenhammer anal speculum (Seward, London, UK) and a 2/0 polyglactin suture on a 25-mm heavy taper-cut needle (Vicryl, W9350; Ethicon, Edinburgh, UK). A loop ileostomy was fashioned in all but two patients, in whom a short mesentery precluded a tension-free stoma. Patients received intraoperative subcutaneous heparin 5000 units or enoxaparin 20 mg, and perioperative intravenous antibiotics.

All patients were followed in the outpatient clinic. Additional functional information was obtained by postal questionnaire and telephone interview. The frequency of defaecation per 24 h and at night was recorded.

The degree of continence was graded as normal, minor incontinence or major incontinence using standard clinical criteria[9,10]. The ability to defer defaecation was assessed as 5 min or less, 5–10 min, 10–20 min, 20–30 min, and more than 1 h.

Results

The median age of the 22 patients undergoing combined abdominoanal revisional surgery was 38 (range 21–54) years. There was no operative death. The median duration of operation, including anaesthetic time was 225 (range 170–345) min and the median duration of hospital stay was 15 (range 8–48) days. Elective closure of the loop ileostomy was performed a median of 166 (range 73–449) days after revisional surgery.

In six patients the length of the rectum was not recorded. In the remaining 16 the median length measured from the anorectal junction to the anastomosis was 4 (range 2–8) cm. Three patients had a stenosis of the ileorectal anastomosis and one patient had a fistula from the anastomosis into the vagina.

Table 1 Early and late complications associated with pouch–rectal revision in 22 patients

Complication	No. of patients
Early (in-hospital)	
Pelvic abscess	4 (1)
Small bowel obstruction	1
Wound infection	2
Subphrenic abscess	1
Acute acalculous cholecystitis	1
High-output ileostomy	2
Late (after discharge)	
Chronic pelvis abscess	2 (1)
Pouch–perianal fistula	2
Anastomotic stenosis	7
Pouchitis	2
Dysfunction	5 (3)

Values in parentheses are the numbers of pouches removed

Early complications *(Table 1)*

In one patient the pouch was excised 37 days after revisional surgery owing to anastomotic failure with pelvic sepsis. Four patients required further surgery including drainage of a left subphrenic collection (n = 1) and endoanal drainage of a pelvic abscess (n = 2). Another patient underwent cholecystectomy for acalculous cholecystitis 16 days after pouch revision.

Late complications *(Table 1)*

Four patients subsequently had the pouch excised, one owing to chronic pelvic sepsis and three to pouch dysfunction. Seven patients developed anastomotic stenosis requiring dilatation, repeated in four patients, under general anaesthesia.

Pouch function *(Table 2; Fig. 1)*

Seventeen patients were available for functional assessment. The median duration of follow-up was 22·5 (range 4–114) months. Before salvage surgery 12 patients had had major incontinence and 13 patients had been unable to defer defaecation for more than 10 min, compared with only four patients after operation. After surgery, ten patients were fully continent during the entire 24-h period. Seven patients were able to defer for more than 1 h. Regular use of antidiarrhoeal medication was required in nine patients. Five patients always wore a pad. Median 24 h frequency before and after operation was 12 (range 4–20) and 6 (range 3–12) respectively. Median night-time frequency before

Table 2 Long-term functional outcome in 17 patients undergoing ileal pouch–rectal revision at a median of 22·5 (range 4–114) months

	Daytime		Night-time	
	Before	After	Before	After
Stool frequency*	12 (4–20)	6 (3–12)	4 (0–8)	0·5 (0–4)
Continence				
Total control	5	11	3	10
Minor incontinence	4	5	2	5
Major incontinence	8	1	12	2
Antidiarrhoeal medication				
Never	5	6		
Occasional	1	2		
Regular × 1 medication	4	8		
Regular × 2 medication	4	1		
Regular × 3 medication	3	0		
Use of pads				
Never	7	10	5	9
Sometimes	1	1	0	2
Frequently	1	1	0	1
Always	8	5	12	5
Urgency				
Able to defer defaecation for more than 60 min	2	7		
Able to defer defaecation for 20–30 min	2	4		
Able to defer defaecation for 10–20 min	0	2		
Able to defer defaecation for 5–10 min	4	4		
Unable to defer defaecation for more than 5 min	9	0		
Perianal irritation				
Never	4	7		
1–2 episodes per week	3	7		
Every day	10	3		
Quality of life				
Excellent	0	4		
Good	0	9		
Reasonable	0	2		
Poor	17	2		
Improved	—	15		

*Median (range) values are given for 24 h and at night, before and after revisional surgery

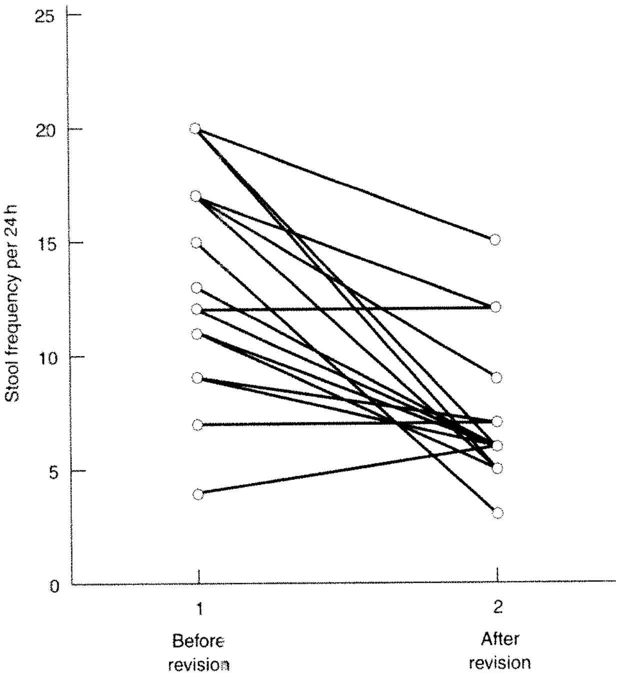


Fig. 1 Stool frequency per 24 h before and after pouch–rectal revision in 17 patients with an intact pouch and anal function

and after operation was 4 (range 0–8) and 0·5 (range 0–4) respectively. Fifteen patients reported subjective improvement in pouch function and quality of life, and two reported no change.

Discussion

There are four general causes of failure after restorative proctocolectomy. These include sepsis, which is responsible for 50 per cent or more failures[11–16], dysfunction, mucosal inflammation and neoplastic transformation. The last two causes are infrequent, especially neoplastic transformation which is exceedingly uncommon[17–21].

Dysfunction accounts for up to 40 per cent of failures[13–16] and has many causes including inflammation, weak sphincter, persisting sepsis, presumed motility disturbances despite no apparent abnormality, and mechanical outflow obstruction. It is important to recognize this last group of patients as surgical correction may be beneficial. There are three causes, including stenosis of the ileoanal anastomosis, impedance to evacuation by, for example, the distal ileal segment of an S reservoir, and retained rectum.

A retained rectal stump causes persisting symptoms of proctitis – mainly bleeding, burning and urgency. It is also associated with the frequent passage of small volumes of stool as a result of incomplete evacuation.

All patients in this series had had a stapled anastomosis. In some patients with a narrow pelvis it can be difficult to dissect the rectum to the anorectal junction and then to apply a transverse stapler at this level. Retained inflamed anorectal mucosa appears to be common after stapling. Lavery *et al.*[2] reported 217 patients having a stapled anastomosis, of whom 48 (22·1 per cent) had evidence of persistently inflamed mucosa distal to the anastomosis. Of these patients, 32 (14·7 per cent of the total) were symptomatic and 28 (12·9 per cent) needed treatment. As the original aim of restorative proctocolectomy is to remove all disease-prone tissue, this could be regarded as inadequate treatment of the disease and would not have arisen if a manual ileoanal anastomosis had been performed. It is certainly a potential disadvantage of stapling.

The results of salvage surgery in this series are worse than would be expected in a series of patients having restorative proctocolectomy for the first time[1,11,12,22–25]. This emphasizes the need for correct technique during the initial operation, as leaving inflamed anorectal mucosa runs the risk of persistent symptoms with the added problem of failure of evacuation.

In essence, the operative decision is between stapled or manual ileoanal anastomosis. Restorative proctocolectomy, as originally described, employed a manual anastomosis as a result of the development of the endoanal technique by Parks *et al.*[26,27]. Subsequently, stapled ileoanal anastomosis was described, with the claim of improved function using this technique[28,29]. These reports were, however, uncontrolled and none of the three randomized controlled trials comparing stapled *versus* manual anastomosis showed a significant difference in complications or function[30–32]. In some patients, achieving an anastomosis at the anorectal junction by stapling may not be possible, as Seow-Choen *et al.*[30] showed in two of 17 patients. Conversely, in a few patients the lack of mobility of the small intestinal mesentery may run the risk of excessive tension if a manual anastomosis is performed within the anal canal, and in this situation a stapled anastomosis may be the only feasible technique to restore intestinal continuity.

The surgeon who routinely uses a stapled technique should therefore recognize that in some patients, usually those with a narrow pelvis, it may not be possible to carry out an anastomosis sufficiently distal to ensure adequate removal of the disease. In this circumstances a manual technique should be used. This is particularly so if severe inflammation in the anorectal mucosa is present. In contrast, the surgeon who routinely employs a manual anastomosis must recognize those patients in whom there may be tension owing to a short mesentery, and be prepared to use a stapled technique. It follows, therefore, that the surgeon should be competent at performing either technique of anastomosis.

The present study reports on a group of patients who had inadequate removal of disease through an anastomosis proximal to persisting inflammation. In these patients local symptoms and poor evacuation necessitated further surgery. Essentially this takes the form of a repeated major procedure similar to the first. The outcome is worse than if the initial operation had adequately removed the diseased mucosa. Thus, of the 22 patients having abdominal salvage procedures, only 15 had a satisfactory or good outcome. When performing restorative proctocolectomy, therefore, the anastomosis should be truly ileoanal, whether by hand suture or by stapling.

References

1 Dozois RR, Goldberg SM, Rothenberger DA, Utsunomiya J, Nicholls RJ, Cohen Z *et al.* Restorative proctocolectomy with ileal reservoir. *Int J Colorectal Dis* 1986, **1:** 2–19.

2 Lavery IC, Sirimarco MT, Ziv Y, Fazio VW. Anal canal inflammation after ileal pouch–anal anastomosis. The need for treatment. *Dis Colon Rectum* 1995; **38:** 803–6.

3 Williams NS. Restorative proctocolectomy is the first choice elective surgical treatment for ulcerative colitis. *Br J Surg* 1989; **76:** 1109–10.

4 Kelly KA. Anal sphincter-saving operations for chronic ulcerative colitis. *Am J Surg* 1992; **163:** 5–11.

5 Becker JM. Surgical management of inflammatory bowel disease. *Curr Opin Gastroenterol* 1993; **9:** 600–15.

6 Pescatori M, Manhire A, Bartram CI. Evacuation pouchography in the evaluation of ileoanal reservoir function. *Dis Colon Rectum* 1983; **26:** 365–8.

7 Herbst F, Sielezneff I, Nicholls RJ. Salvage surgery for ileal pouch-outlet obstruction. *Br J Surg* 1996; **83:** 368–71.

8 Lee ECG, Dowling BL. Perimuscular excision of the rectum for Crohn's disease and ulcerative colitis. A conservation technique *Br J Surg* 1972; **59:** 29–32.

9 Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72:** 470–4.

10 Nasmyth DG, Williams NS, Johnston D. Comparison of the function of triplicated and duplicated pelvic ileal reservoirs after mucosal proctectomy and ileo-anal anastomosis for ulcerative colitis and adenomatous polyposis. *Br J Surg* 1986; **73:** 361–6.

11 Setti Carraro P, Ritchie JK, Wilkinson KH, Nicholls RJ, Hawley PR. The first 10 years' experience of restorative proctocolectomy for ulcerative colitis. *Gut* 1994; **35:** 1070–5.

12 Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch–anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. *Br J Surg* 1998; **85:** 800–3.

13 Gemlo BT, Wong WD, Rothenberger DA, Goldberg SM. Ileal pouch–anal anastomosis. Patterns of failure. *Arch Surg* 1992; **127:** 784–7.

14 Foley EF, Schoetz DJ Jr, Roberts PL, Marcello PW, Murrey JJ, Coller JA *et al.* Rediversion after ileal pouch–anal anastomosis. Causes of failures and predictors of subsequent pouch salvage. *Dis Colon Rectum* 1995; **38:** 793–8.

15 MacRae HM, McLeod RS, Cohen Z, O'Connor BI, Ton ENC. Risk factors for pelvic pouch failure. *Dis Colon Rectum* 1997; **40:** 257–62.

16 Galandiuk S, Scott NA, Dozois RR, Kelly KA, Ilstrup DM, Beart RW Jr *et al.* Ileal pouch–anal anastomosis. Reoperation for pouch-related complications. *Ann Surg* 1990; **212:** 446–54.

17 Tsunoda A, Talbot IC, Nicholls RJ. Incidence of dysplasia in

the anorectal mucosa in patients having restorative proctocolectomy. *Br J Surg* 1990; **77:** 506–8.
18 Ziv Y, Fazio VW, Sirimarco MT, Lavery IC, Goldblum JR, Petras RE. Incidence, risk factors, and treatment of dysplasia in the anal transitional zone after ileal pouch–anal anastomosis. *Dis Colon Rectum* 1994; **37:** 1281–5.
19 Veress B, Reinholt FP, Lindquist K, Lofberg R, Liljeqvist L. Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. *Gastroenterology* 1995; **109:** 1090–7.
20 Setti Carraro P, Talbot IC, Nicholls RJ. Longterm appraisal of the histological appearances of the ileal reservoir mucosa after restorative proctocolectomy for ulcerative colitis. *Gut* 1994; **35:** 1721–7.
21 Tarroni D, Wilkinson KH, Tulchinsky H, Rumbles SW, Talbot IC, Nicholls RJ. Long-term outcome after ileoanal pouch for inflammatory bowel disease (IBD). *Colorectal Disease* 2000; **2**(Suppl 1): 24 (Abstract).
22 Marcello PW, Roberts PL, Schoetz DJ, Coller JA, Murray JJ, Veidenheimer MC. Long-term results of the ileoanal pouch procedure. *Arch Surg* 1993; **128:** 500–4.
23 Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW *et al.* Ileal pouch–anal anastomosis complications and function in 1005 patients. *Ann Surg* 1995; **222:** 120–7.
24 Dayton MT, Larsen KP. Outcome of pouch-related complications after ileal pouch–anal anastomosis. *Am J Surg* 1997; **174:** 728–32.
25 Pezim ME, Nicholls RJ. Quality of life after restorative proctocolectomy with pelvic ileal reservoir. *Br J Surg* 1985; **72:** 31–3.
26 Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. *BMJ* 1978; **ii:** 85–8.
27 Parks AG, Nicholls RJ, Belliveau P. Proctocolectomy with ileal reservoir and anal anastomosis. *Br J Surg* 1980; **67:** 533–8.
28 Heald RJ, Allen DR. Stapled ileo-anal anastomosis: a technique to avoid mucosal proctectomy in the ileal pouch operation. *Br J Surg* 1986; **73:** 571–2.
29 Johnston D, Holdsworth PJ, Nasmyth DG, Neal DE, Primrose JN, Womack N *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. *Br J Surg* 1987; **74:** 940–4.
30 Seow-Choen A, Tsunoda A, Nicholls RJ. Prospective randomized trial comparing anal function after hand sewn ileoanal anastomosis with mucosectomy *versus* stapled ileoanal anastomosis without mucosectomy in restorative proctocolectomy. *Br J Surg* 1991; **78:** 430–4.
31 Luukkonen P, Jarvinen H. Stapled *vs* hand-sutured ileoanal anastomosis in restorative proctocolectomy. A prospective, randomized study. *Arch Surg* 1993; **128:** 437–40.
32 Reilly WT, Pemberton JH, Wolff BG, Nivatvongs S, Devine RM, Litchy WJ *et al.* Randomized prospective trial comparing ileal pouch–anal anastomosis performed by excising the anal mucosa to ileal pouch–anal anastomosis performed by preserving the anal mucosa. *Ann Surg* 1997; **225:** 666–77.

Original article

Impact of total mesorectal excision on the results of surgery of distal rectal cancer

W. L. Law and K. W. Chu

Department of Surgery, Queen Mary Hospital, University of Hong Kong Medical Centre, 102 Pokfulam Road, Hong Kong
Correspondence to: Dr K. W. Chu (e-mail: chukw@hkucc.hku.hk)

Background: This study reviewed the results of surgery for distal rectal cancer (tumours within 6 cm of the anal verge) following the introduction of total mesorectal excision for rectal cancer in one institution.

Methods: Two hundred and five patients who had undergone surgical resection of rectal cancer within 6 cm of the anal verge were included. The demographic, operative and follow-up data were collected prospectively. Comparisons were made between patients who had different surgical procedures.

Results: Abdominoperineal resection (APR) was performed in 27·8 per cent of patients, falling from 36·0 per cent in the first 3 years to 20·0 per cent in the last 3 years of the study. The overall operative mortality rate was 1·5 per cent and the morbidity rate 30·2 per cent. With a mean follow-up of 36 months, local recurrence occurred in 28 of the 185 patients who had curative resection. The 5-year actuarial local recurrence rates for double-stapled anastomosis, peranal coloanal anastomosis and APR were 11·2, 34·6 and 23·5 per cent respectively. The local recurrence rate was significantly lower for double-stapled low anterior resection than for the other types of operation. The overall 5-year survival rate in patients with low anterior resection and APR was 69·1 and 51·1 per cent respectively ($P = 0.12$).

Conclusion: With the practice of total mesorectal excision, APR was necessary in only 27·8 per cent of patients with rectal cancer within 6 cm of the anal verge. The local recurrence rate was much lower in patients with double-stapled low anterior resection than in those treated with APR or peranal anastomosis.

Paper accepted 25 July 2001

British Journal of Surgery 2001, 88, 1607–1612

Introduction

Abdominoperineal resection (APR) has been the standard treatment of rectal cancer since its description by Miles[1] at the beginning of the last century. With advances in the techniques for rectal anastomosis, anterior resection with preservation of sphincter function has become the usual treatment for cancers of the upper and mid rectum. The advent of mechanical stapling devices and the double-stapling technique has rendered anastomosis at the distal rectum or anal canal technically easier. Local recurrence has, however, always been a problem in the management of rectal cancer. In the 1980s and early 1990s, local recurrence rates of 20–30 per cent were reported[2–5]. The importance of the mesorectum in local recurrence has recently been emphasized[6]. Local recurrence rates of less than 5 per cent have been reported with a distal mural margin of less than 1 cm, provided the mesorectum could be excised entirely[7]. APR is now reserved only for distal rectal cancer where anastomosis is not possible. Previous comparison of the surgical results of APR with those of low anterior resection (LAR) in patients with rectal cancers at all levels, including those at the mid rectum, upper rectum or even rectosigmoid, is no longer valid as tumours at these levels are seldom treated with sphincter ablation.

Total mesorectal excision (TME) has become the standard treatment for rectal cancer in the authors' department since September 1993. In this study, the results of patients who had undergone resection of distal rectal cancer were analysed to compare the outcome of operations for the treatment of rectal tumours at levels that would ordinarily require sphincter ablation.

Patients and methods

From September 1993 the senior author (K.W.C.) adopted the technique of TME for curative radical resection of rectal cancers within 12 cm of the anal verge. The demographic data, operative details, postoperative events and follow-up data of the patients were entered prospectively into the rectal cancer database. Up to June 2000, a total of 394 patients underwent resection for rectal cancer within 12 cm from the anal verge. Of these, 205 patients had distal rectal cancer with the distal border within 6 cm of the anal verge. These patients are the subject of this study.

All patients had preoperative endoscopy with histologically proven adenocarcinoma of rectum. The details of the operative technique of LAR, with either double stapling or transanal coloanal anastomosis, have been published previously[8]. In essence, rectal mobilization was carried out by sharp dissection under direct vision keeping the fascia propria of the mesorectum intact. Double stapling was considered possible when an adequate resection margin could be obtained and an adequate healthy rectal stump was present for anastomosis with the circular stapler.

In the initial period a policy of selective faecal diversion for high-risk anastomoses was adopted and loop ileostomy was the preferred mode of proximal diversion. A loop transverse colostomy was constructed when patients had radiation enteritis or an ileal conduit was to be constructed after concomitant total cystectomy. Later patients were randomized to loop transverse colostomy or loop ileostomy as part of an ongoing trial. After interim analysis of the risk factors for anastomotic leakage[8], a proximal diversion was routinely performed in men following TME and an anastomosis within 5 cm of the anal verge.

In transanal coloanal anastomosis, the perineal surgeon completed the excision transanally at the dentate line. A hand-sewn single-layer interrupted anastomosis was performed transanally. A colonic J pouch of 5 cm was created in most patients. A diverting stoma was constructed routinely in this group of patients.

Adjuvant postoperative radiation was not given routinely to patients after LAR with TME. Postoperative chemotherapy was offered to patients under the age of 70 years with stage II or III disease, and later in the study to those aged less than 75 years. Preoperative chemoradiotherapy was used in patients with fixed tumours (T_4) diagnosed before operation during the latter part of the study.

APR was performed in patients with tumours at a level at which the anal sphincter muscles could not be spared. A two-team approach was used and a laparoscopic approach was performed in selected cases. Abdominal mobilization of the rectum was carried out in the same manner as in LAR using the TME technique, in both the open and the laparoscopic approach. Three patients had coloperineal anastomosis and simultaneous dynamic graciloplasty after APR in 1999. Adjuvant postoperative chemoradiotherapy was offered to patients with stage II and III disease.

The patients were followed at 2–4-month intervals during the first 2 years and at 4–6-month intervals for 3 years thereafter. Follow-up of patients was by history, physical examination and determination of serum carcinoembryonic antigen levels. Computed tomography and colonoscopy were performed when there was suspicion of recurrence and to assess the operability of the recurrence. Local recurrence was defined as histologically or radiologically proven disease in the pelvis within the field of surgery.

Comparison of variables was performed with the χ^2 test and Student's t test for categorical and continuous variables respectively. Actuarial local recurrence and survival was analysed with the Kaplan–Meier method; comparison was made with the log rank test. $P < 0.05$ was considered significant.

Results

From September 1993 to June 2000, 205 patients underwent resection of rectal cancer with the most distal tumour margin within 6 cm of the anal verge. The operation was considered as palliative in 20 patients because of irresectable distant metastasis (n = 11), residual local disease (n = 7) and positive resection margin without further resection (n = 2). Of the 185 patients who underwent potentially curative resection, there were 104 men and 81 women; their mean age was 64·4 (range 33–90) years. The mean level of the most distal tumour margin was 4·4 (range 0–6) cm from the anal verge. The types of operation are shown in *Table 1*. The APR rate reduced from 36·0 per cent in the interval to December 1996, to 20·0 per cent in the period from January 1997 to June 2000. Hartmann's operation was performed in seven patients as a palliative procedure. In six other patients poor sphincter function (n = 2), poor premorbid condition with bulky tumour (n = 3) or intraoperative events (n = 1) were the reasons for resection without anastomosis. Eleven patients underwent potentially curative transanal local excision.

Among patients who had LAR, a double-stapled anastomosis was performed in 98 patients and a hand-sewn peranal coloanal anastomsis in 25. Temporary proximal faecal diversion was performed in 92 patients (74·8 per cent).

Three patients died in the postoperative period, two after palliative Hartmann's operation as a result of advanced malignancy. The other patient died 17 days after LAR from mesenteric thrombosis and small bowel infarction. Thus the operative mortality rate was 1·5 per cent for all patients and 0·5 per cent in patients who underwent curative resection.

Perioperative morbidity occurred in 62 patients (30·2 per cent). Details of the complications are shown in *Table 2*. In

Table 1 Types of operation used in the treatment of 205 patients with distal rectal cancer

	September 1993 to December 1996			January 1997 to June 2000		
	Curative	Palliative	Total	Curative	Palliative	Total
APR	32 (36·4)	4 (33·3)	36 (36·0)	19 (19·6)	2 (25·0)	21 (20·0)
LAR	48 (54·5)	3 (25·0)	51 (51·0)	69 (71·1)	3 (37·5)	72 (68·6)
Hartmann operation	3 (3·4)	4 (33·3)	7 (7·0)	3 (3·1)	3 (37·5)	6 (5·7)
Transanal excision	5 (5·7)	1 (8·3)	6 (6·0)	6 (6·2)	0 (0.0)	6 (5·7)
Total	88 (100)	12 (100)	100 (100)	97 (100)	8 (100)	105 (100)

Values in parentheses are percentages. APR, abdominoperineal resection; LAR, low anterior resection

Table 2 Postoperative complications after operation for distal rectal cancer

	No. of patients
Pneumonia	8
Arrhythmia	6
Urine retention	9
Urinary tract infection	6
Small bowel obstruction or prolonged ileus	7
Deep vein thrombosis	2
Bleeding peptic ulcer	4
Postoperative bleeding	
Anastomotic	2
Intra-abdominal	2
Anastomotic leak	6
Wound infection	13
Pelvic abscess	2
Ischaemic bowel	3
Other	2

Table 3 Comparison of patients undergoing abdominoperineal resection and low anterior resection

	LAR ($n = 123$)	APR ($n = 57$)	P
Sex ratio (M : F)	71 : 52	36 : 21	n.s.*
Mean age (years)	63·6	65·0	n.s.†
Mean level of tumour (cm)	5·1	2·8	0·005†
Curative resection	117 (95·1)	51 (89·5)	n.s.*
Radiotherapy	9 (7·3)	21 (36·8)	< 0·001*
Preop.	7	3	
Postop.	2	18	
Chemotherapy	53 (43·1)	20 (35·1)	n.s.*
Tumour stage			n.s.*
I	21 (17·1)	13 (22·8)	
II	47 (38·2)	13 (22·8)	
III	48 (39·0)	27 (47·4)	
IV	7 (5·7)	4 (7·0)	
Morbidity	37 (30·1)	20 (35·1)	n.s.*
Mortality	1 (0·8)	0 (0·0)	n.s.*

Values in parentheses are percentages. APR, abdominoperineal resection; LAR, low anterior resection; n.s., not significant. *χ^2 test; †t test

the six patients with anastomotic leakage, conservative treatment was possible in four and two required operation because of peritonitis.

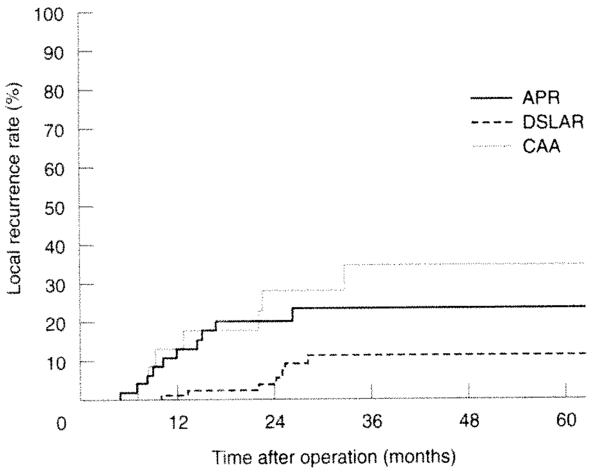
Comparison between patients with LAR and APR is shown in *Table 3*. The mean level of tumours was significantly lower in patients who had APR. More patients in the APR group received adjuvant radiotherapy.

Local recurrence

With a mean follow-up of 36 months in the 185 patients who underwent curative resection, local recurrence occurred in 28 patients. Patients who had a curative Hartmann operation with TME were grouped with those who underwent double-stapled LAR in the subsequent analysis of survival and local recurrence.

Local recurrence occurred in 14 of 123 patients who had LAR or Hartmann's operation with TME (seven with double-stapled anastomosis, seven with peranal coloanal anastomosis), in ten of 51 patients who underwent APR and in four of 11 who had local excision. The 5-year actuarial local recurrence rate was 11·2, 23·5 and 34·6 per cent in double-stapled LAR, APR and peranal colonanal anastomosis respectively. The local recurrence rate was significantly lower in patients who had double-stapled LAR than in those who underwent APR ($P = 0·02$) or peranal coloanal anastomosis ($P = 0·008$) (*Fig. 1*).

In view of the high recurrence rate, patients who had peranal coloanal anastomosis were closely examined. There were 25 patients (18 men and seven women); their mean age was 60 (range 37–76) years and the mean level of tumour was 3·9 cm from the anal verge, which was significantly more distal than the level in patients who underwent double-stapled anastomosis. The mean distal resection margin was 0·81 cm. In one patient the margin was positive,



No. at risk						
CAA	24	22	15	12	6	3
APR	51	45	32	23	16	9
DSLAR	99	77	58	37	27	16

Fig. 1 Local recurrence following different types of operation for distal rectal cancer: APR, abdominoperineal resection; DSLAR, double-stapled low anterior resection; CAA, coloanal anastomosis. $P = 0·02$ (DSLAR *versus* APR); $P = 0·008$ (DSLAR *versus* CAA) (log rank test)

and in the other three patients the resection margin was reported as being close to the tumour. Thus these were patients with very distal tumours in whom the limit of sphincter preservation was stretched in order to avoid sphincter ablation.

Survival

The overall 5-year survival rate of patients who had a curative resection was 64 per cent, whereas the median survival of those who underwent palliative resection was 17·4 months. The overall 5-year survival rate of patients who had LAR and APR was 69·1 and 51·1 per cent respectively ($P = 0·12$). When the survival of patients with LAR was analysed, the overall 5-year survival rate of patients who underwent double-stapled LAR and those who had peranal anastomosis was 70·8 and 66·1 per cent respectively ($P = 0·66$).

Discussion

In the past 20 years the importance of the mesorectum in the treatment of rectal cancer has been recognized[6,9–11]. The concept of TME and the increasing use of stapling devices for distal rectal and anal anastomoses have had a significant impact on the treatment of distal rectal cancer. With the use of TME and a close distal resection margin, the need for sphincter ablation can be reduced. Although APR has been described as standard treatment for tumours less than 8 cm from the anal verge[12], more patients with distal rectal cancer are now being treated with sphincter-saving surgery. Marling *et al.*[13] reported that, with use of TME, the APR rate for all rectal cancers was reduced from 55–60 per cent to 27 per cent. Heald *et al.*[14] showed that only 23 per cent of 136 patients with tumours less than 5 cm from the anal verge required APR. In the present study, only patients with cancers within 6 cm of the anal verge were included. The results show that APR was required in only 27·8 per cent of patients. With increasing experience in TME, the rate of APR reduced from 36·0 per cent in the initial 3 years to 20·0 per cent in the subsequent 3 years. In fact, in the latter part of the study no patient with a tumour more than 4 cm from the anal verge required APR. The high sphincter-preserving rate was achieved by meticulous pelvic dissection to mobilize the rectum with the entire mesorectum down to the pelvic floor and use of the double-stapling technique to perform a low anastomosis. In addition, when it was impossible to use a double-stapling technique, peranal anastomosis was performed. Subsequent outcome has shown that this practice is associated with an increased local recurrence rate. It did, however, provide an option for patients who were reluctant to have a permanent stoma.

In this study the operative mortality rate was low and compared favourably with that of other series of TME[9,13,15–17]. Intraoperative complications were rare. However, anastomotic leakage remained a problem following LAR. The authors have previously reported a 10·2 per cent leakage rate in 196 patients with an anastomosis within 5 cm of the anal verge[8], comparable to the results of Karanjia *et al.*[18]. Male sex and the absence of proximal diversion were identified as the two independent factors associated with anastomotic leakage. In this series of low rectal cancers, proximal diversion was performed in 74·8 per cent of patients and anastomotic leakage occurred in only six of the 123 patients with anastomosis.

Local recurrence is an important indicator of the success of rectal surgery. Wide variations in the incidence of local recurrence have been reported. With the advent of TME, most series have reported a local recurrence rate of about 10 per cent or less[9,10,13,15,19], lower than that in the surgery-alone arm in most adjuvant therapy trials[20–22]. Before the era of TME, most reports comparing LAR and APR showed no differences in local recurrence[2,5,23–25]. Many of these series included patients with rectal cancers at all levels, and the proportion of APR was in the range of 30–50 per cent[2,23,24]. Two series with more than 1000 patients showed that patients with tumours in the upper rectum had a better outcome[2,26]. In order to have a fair comparison between APR and LAR, only patients with distal rectal cancer were included in the present study. With a mean follow-up of 36 months, 28 (15·1 per cent) of 185 patients developed local recurrence. The apparently high local recurrence rate may be due to exclusion of patients with upper and mid rectal cancers. Patients who had double-stapled anastomosis had a significantly better outcome than those who underwent APR or peranal anastomosis. Although the survival rates of patients having APR and double-stapled LAR did not show any difference, this might be due to the relatively short length of follow-up. Heald *et al.*[14] found a 6-year actuarial local recurrence rate of 33 per cent after curative APR, compared with 4 per cent in patients with anterior resection. The 5-year actuarial local recurrence rate after APR was 23·5 per cent in the present study, confirming that APR could not prevent local recurrence even though an apparently wider excision had been performed. Heald *et al.*[14] postulated that the break in the pelvic floor and the creation of the perineal wound provided an opportunity for the implantation or downgrowth of tumour cells.

Poor local control also occurred in the patients who had peranal coloanal anastomosis, when the transverse stapler could not be applied to the rectal stump with an adequate distal margin. The mean distal tumour margin in these patients was 0·81 cm and there was no additional resection margin provided by the distal doughnut of tissue created by the circular stapler. However, the difference in local recurrence might be a reflection of the tumour rather than the type of operation. Karanjia *et al.*[7] claimed that if TME and double-stapled anastomosis could be performed local recurrence could be kept at a low rate, as long as the distal margin was less than 1 cm. However, the high local recurrence rate in patients with APR in their series probably reflected that tumours at that level might perform badly. In the present study it was shown that cancers at the distal rectum that could not be treated by the double-stapling technique were associated with a high local recurrence rate; these patients may require neoadjuvant treatment to reduce local recurrence.

In conclusion, TME with anterior resection reduces the need for anal sphincter ablation. Double-stapled anastomosis with TME can achieve low recurrence rates without routine radiation therapy in patients with distal rectal cancer. In patients with very distal rectal cancers that could not treated by means of double stapling, peranal coloanal anastomosis with a close resection margin is associated with a higher local recurrence rate than double-stapled LAR or APR. Thus a patient who cannot be treated with double-stapled LAR should have an APR until there is evidence that the local recurrence rate of peranal anastomosis can be reduced with adjuvant therapy.

References

1 Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and the terminal portion of the pelvic colon. *Lancet* 1908; ii: 1812–13.
2 McDermott FT, Hughes ES, Pihl E, Johnson WR, Price AB. Local recurrence after potentially curative resection for rectal cancer in a series of 1008 patients. *Br J Surg* 1985; **72:** 34–7
3 Adloff M, Arnaud JP, Schloegel M, Thibaud D. Factors influencing local recurrence after abdominoperineal resection for cancer of the rectum. *Dis Colon Rectum* 1985; **28:** 413–15
4 Pakkastie TE, Luukkonen PE, Jarvinen HJ. Anterior resection controls cancer of the rectum as well as abdominoperineal excision. *Eur J Surg* 1995; **161:** 833–9.
5 Nymann T, Jess P, Christiansen J. Rate and treatment of pelvic recurrence after abdominoperineal resection and low anterior resection for rectal cancer. *Dis Colon Rectum* 1995; **38:** 799–802.
6 Scott N, Jackson P, al Jaberi T, Dixon MF, Quirke P, Finan PJ. Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. *Br J Surg* 1995; **82:** 1031–3.
7 Karanjia ND, Schache DJ, North WR, Heald RJ. 'Close shave' in anterior resection. *Br J Surg* 1990; **77:** 510–12.
8 Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. *Am J Surg* 2000; **179:** 92–6.
9 Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995; **181:** 335–46.
10 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; i: 1479–82.
11 McCall JL. Total mesorectal excision: evaluating the evidence. *Aust N Z J Surg* 1997; **67:** 599–602.
12 Corman ML. Carcinoma of the rectum. In: *Colon and Rectal Surgery*. 4th ed. Philadelphia, Pennsylvania: Lippincott-Raven, 1998: 733–862.
13 Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; **356:** 93–6.
14 Heald RJ, Smedh RK, Kald A, Sexton R, Moran BJ. Abdominoperineal excision of the rectum – an endangered operation. Norman Nigro Lectureship. *Dis Colon Rectum* 1997; **40:** 747–51.
15 Arenas RB, Fichera A, Mhoon D, Michelassi F. Total mesenteric excision in the surgical treatment of rectal cancer: a prospective study. *Arch Surg* 1998; **133:** 608–11.
16 Bolognese A, Cardi M, Muttillo IA, Barbarosos A, Bocchetti T, Valabrega S. Total mesorectal excision for surgical treatment of rectal cancer. *J Surg Oncol* 2000; **74:** 21–3.
17 Carlsen E, Schlichting E, Guldvog I, Johnson E, Heald RJ.

Effect of the introduction of total mesorectal excision for the treatment of rectal cancer. *Br J Surg* 1998; **85:** 526–9.

18 Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. *Br J Surg* 1994; **81:** 1224–6.

19 Arbman G, Nilsson E, Hallbook O, Sjodahl R. Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg* 1996; **83:** 375–9.

20 Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL *et al.* Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988; **80:** 21–9.

21 Gerard A, Buyse M, Nordlinger B, Loygue J, Pene F, Kempf P *et al.* Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988; **208:** 606–14.

22 Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW *et al.* Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; **324:** 709–15.

23 Heimann TM, Szporn A, Bolnick K, Aufses AH Jr. Local recurrence following surgical treatment of rectal cancer. Comparison of anterior and abdominoperineal resection. *Dis Colon Rectum* 1986; **29:** 862–4.

24 Amato A, Pescatori M, Butti A. Local recurrence following abdominoperineal excision and anterior resection for rectal carcinoma. *Dis Colon Rectum* 1991; **34:** 317–22.

25 Vlasak JW, Wagner D, Passaro E Jr, Wilson SE. Local recurrence after curative resection of rectal cancer: a comparison of low anterior resection and abdominoperineal resection. *J Surg Oncol* 1989; **41:** 236–9.

26 Lopez-Kostner F, Lavery IC, Hool GR, Rybicki LA, Fazio VW. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery* 1998; **124:** 612–17.

Original article

Systemic levels of glyceryl trinitrate following topical application to the anoderm do not correlate with the measured reduction in anal pressure

M. Jonas, D. A. Barrett*, P. N. Shaw* and J. H. Scholefield

Departments of Surgery and *Pharmaceutical Sciences, University of Nottingham, Nottingham, UK
Correspondence to: Professor J. H. Scholefield, Section of Surgery, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK
(e-mail: John.Scholefield@nottingham.ac.uk)

Background: Topical 0·2 per cent glyceryl trinitrate (GTN) lowers resting anal pressure (RAP) and heals two-thirds of chronic anal fissures. Over 50 per cent of patients experience headache, presumably through systemic absorption, but the pharmacokinetics of GTN ointment are unknown. This study evaluated the systemic absorption profile of GTN, and correlation between plasma GTN levels, RAP, haemodynamic variables and side-effects.

Methods: Thirty healthy volunteers were recruited with local medical school ethics committee approval. Continuous static anal manometry was performed for 10 min before and 2 h after application of 0·2 per cent GTN (0·5 g) to the anoderm. Blood samples were taken from an intravenous cannula, and pulse and blood pressure were measured before application of GTN, and 10, 20, 30, 40, 50, 60, 90, 120 and 180 min thereafter. Details of side-effects were recorded.

Results: GTN was detected in the plasma 10 min to 3 h after topical application. RAP was significantly reduced after 10 min, but had returned to pretreatment values by 120 min. Pulse was statistically unchanged during the study; systolic blood pressure was significantly lower 20–90 min after GTN application, and diastolic pressure was decreased throughout the study. Headaches were experienced by 14 of 30 volunteers after a median (range) of 41 (4–120) min, persisting for 74 (30–176) min, with an intensity score of 19 (5–30) mm represented on a 100-mm linear visual analogue scale. There was no correlation between plasma GTN concentration, RAP, and the onset, duration or intensity of headaches.

Conclusion: Topical GTN acts locally on the internal anal sphincter; systemic levels do not contribute significantly to the reduction in RAP. There is marked interindividual variation in plasma GTN levels, and no correlation with haemodynamic variables and side-effects.

Presented to the Association of Surgeons of Great Britain and Ireland, Birmingham, UK, April 2001, and published in abstract form as *Br J Surg* 2001; 88(Suppl 1): 72

Paper accepted 10 August 2001

British Journal of Surgery 2001, 88, 1613–1616

Introduction

Topical 0·2 per cent glyceryl trinitrate (GTN) ointment applied to the anal verge is now widely accepted as a first-line treatment for chronic anal fissure. GTN is metabolized at a cellular level to release nitric oxide, a non-adrenergic non-cholinergic neurotransmitter that mediates relaxation of the internal anal sphincter (IAS)[1,2]. In this way GTN lowers resting anal pressure (RAP) and effectively produces a chemical sphincterotomy. A regimen of 0·2 per cent GTN applied twice daily to the anal verge heals two-thirds of chronic anal fissures within 8 weeks[3–5].

Unfortunately, over 50 per cent of patients experience troublesome headaches with this treatment[3–5], presumably because of systemic absorption of GTN from the anal mucosa and perianal skin. The strategy of using GTN at higher concentrations to improve healing rates is not feasible as side-effects occur even more frequently[6,7]. The profile of absorption of GTN into the bloodstream following topical application to the anal verge is unknown, as is the contribution of systemic GTN to the reduction in RAP. There may also be a correlation between plasma concentration of GTN and the onset and duration of side-effects, but this remains to be evaluated.

The first aim of this study was to evaluate the profile of systemic absorption of topical 0·2 per cent GTN following its application to the anoderm. The second objective was to determine any correlation between plasma concentrations of GTN, RAP, haemodynamic variables, and the onset, duration and intensity of side-effects.

Materials and methods

Ethics committee approval was obtained and 30 healthy volunteers gave informed consent to participate in the study. An intravenous cannula was positioned in one antecubital fossa to allow blood samples (5 ml each time) to be taken before, every 10 min for the first hour, and then at 90, 120 and 180 min after the application of GTN. These ten samples meant that a total volume of 50 ml was taken. Blood was transferred immediately from the plastic syringe to silane-coated glass tubes containing heparinized saline (50 units heparin in 50 μl saline) and centrifuged at 1800 r.p.m. for 8 min. Plasma (1 ml) was then added to each of two fresh silane-coated tubes, snap frozen in liquid nitrogen and stored at −80°C until analysis for concentrations of GTN. Analysis for GTN was conducted in duplicate by an independent technician, using a gas chromatography–electron capture detection method capable of detecting 20 pg/ml of GTN in plasma[8].

Continuous static anal manometry was performed, with volunteers lying on one side, using a solid-state catheter (Gaeltec, Isle of Skye, UK). A station pull-through technique was used to position the catheter to record maximal RAP for 10 min before and 2 h after application of 1 cm (approximately 0·5 g) of 0·2 per cent GTN ointment (2 per cent Percutol® (Cusi, Hazelmere, UK) diluted to 0·2 per cent in soft white paraffin in the pharmacy). The manometry catheter was secured in place with adhesive tape to the buttock, a short distance from the anal margin, and its position checked both following application of GTN ointment and at the end of the study period. Subjects were asked to apply GTN circumferentially 1 cm inside the anus using a gloved finger. Anal pressures for each of the four radial pressure sensors on the anal manometry catheter were determined from the pressure trace by an independent assessor. The mean anal pressure over a 10-min period centred on times 0, 10, 20, 30, 40, 50, 60, 90 and 120 min was calculated using Flexisoft III software (Oakfield Instruments, Whitney, UK). A mean of these four values was then calculated to give a single value for RAP at each time interval.

Measurements of pulse and blood pressure were recorded, with subjects lying on their sides, before application of GTN and then at intervals corresponding to the times of blood sampling. At the beginning of the study volunteers were asked to report any side-effects they might experience following administration of GTN and were reminded to do this throughout the study. The onset and duration of side-effects were recorded, and subjects were asked to represent the intensity of headaches using linear visual analogue scales (unmarked 100-mm lines, where the left end represented no symptoms and the right end the worst symptoms imaginable).

Statistical analysis

Statistical analysis was with Wilcoxon signed rank test to compare RAPs, plasma concentrations of GTN and haemodynamic variables before and after the application of GTN. Pearson's correlation test was used to determine any correlation between the onset and duration of headaches, plasma concentrations of GTN, changes in haemodynamic variables and RAP.

Results

Thirty healthy volunteers (18 men) with a median (range) age of 35 (20–72) years were included in the study. GTN was detected in the plasma from 10 min to 3 h after topical administration to the distal anal canal. The duplicate values for plasma GTN concentrations were normally within 10 per cent of one another. The maximal mean plasma concentration of GTN was 158 pg/ml, observed 90 min following application, but there was no statistically significant difference between the plasma concentrations of GTN at different times of blood sampling following application (*Fig. 1*).

Topical 0·2 per cent GTN caused a maximal reduction in RAP of 41 per cent from a median (range) of 66 (35–95) to 39 (10–71) cmH_2O. A significant decrease in RAP was observed from 10 until 90 min after application of GTN; by 120 min the RAP was no longer statistically different to that measured before application of GTN.

The radial pulse rate did not change significantly during the study. Systolic blood pressure was significantly reduced after 20 min but had returned to original values by 120 min; diastolic pressure had dropped significantly by 10 min after application of GTN and this effect was maintained throughout the study.

Headaches were experienced by 14 volunteers and were the only side-effect reported during the study. The median (range) time to onset of headache following application of GTN was 41 (4–120) min, the duration was 74 (30–176) min and the intensity was 19 (5–30) mm on a linear visual analogue scale.

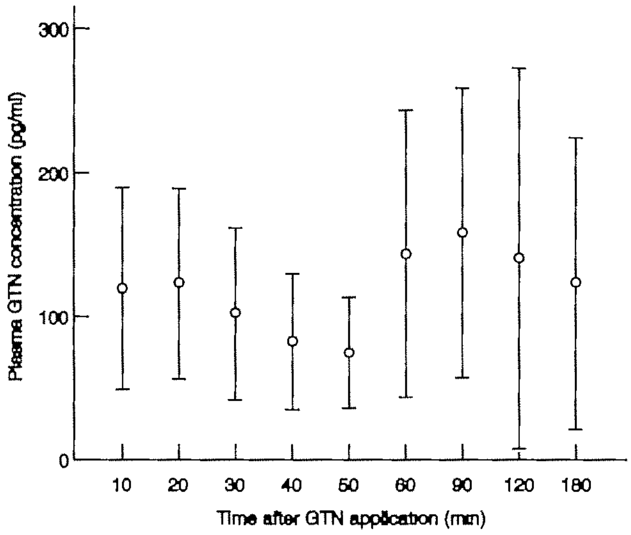


Fig. 1 Plasma concentrations of glyceryl trinitrate (GTN) following topical application of 0·2 per cent ointment (0·5 g) to the anal verge. Mean values are shown with 95 per cent confidence intervals

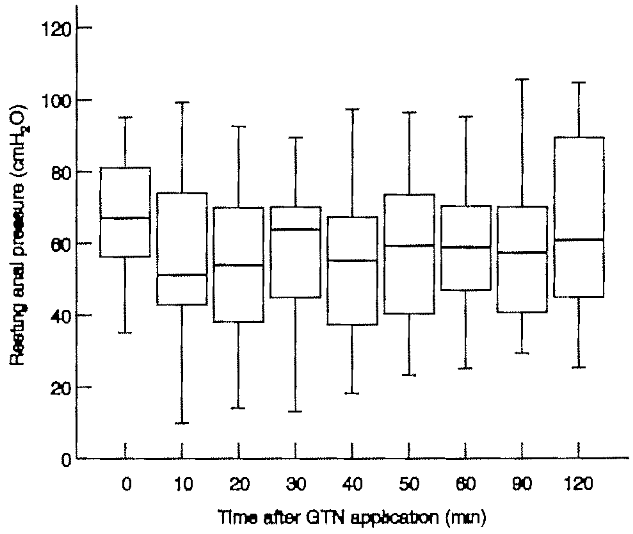


Fig. 2 Resting anal pressure before (time zero) and at intervals following the application of 0·2 per cent glyceryl trinitrate (GTN) ointment (0·5 g) to the anal margin. Resting anal pressure was significantly reduced by 10 min ($P = 0·001$, Wilcoxon signed rank test) and this effect was maintained until 90 min after application of GTN. By 120 min there was no longer a significant reduction in pressure compared with baseline values. Horizontal bars represent the median and interquartile range

There was no correlation between plasma concentrations of GTN, haemodynamic variables, RAP, or the onset, duration and intensity of the headaches.

Discussion

This study found considerable interindividual variation between plasma concentrations of GTN following application of 0·5 g of 0·2 per cent GTN ointment to the distal anal canal. There was substantial variability in the maximum plasma GTN concentration and the time to reach maximum concentration, although measurable GTN levels were maintained in all patients during the course of the study. This may be explained by a number of factors, including variation in the intra-anal dose, variation in absorption across anal mucosa and perianal skin, and differences in rates of metabolism and sensitivity to GTN. Absorption across the anal mucosa is likely to be faster than that across perianal skin; skin thicknesses are variable and have been shown to influence rates of absorption[9]. None the less, the mean plasma GTN concentrations were fairly constant during the study; the maximal mean plasma concentration of GTN was 158 pg/ml, observed after 90 min, but was not significantly higher than levels observed at other times.

In contrast to the steady plasma GTN concentrations measured during the study, RAP was significantly decreased 10 min after application of GTN, but had returned to baseline values by 120 min (*Fig. 2*). Topical 0·2 per cent GTN therefore appears to act locally on the IAS, with systemic levels having a negligible effect. Reports of the duration of action of GTN on the IAS following topical application are few in number and their findings conflict. One study reported the mean duration of effect of GTN on RAP to be 48 min following intra-anal application of 5 mg of 2 per cent GTN in 38 patients, while another group observed that RAP remained lowered for 9 h in two patients following external application of an unspecified dose of 0·2 per cent GTN[10,11]. The findings of this study, however, are consistent with one other report in which 0·2 per cent GTN was similarly applied both intra-anally and to the perianal skin, and monitoring of anal pressure was continuous and not by interrupted measurements[12].

Approximately half of the volunteers in this study experienced headache following application of GTN, which is in keeping with previous reports in patients[3,5], but there was no demonstrable correlation between the onset, intensity or duration of headache, haemodynamic variables and plasma concentrations of GTN. Volunteers were reminded throughout the study to report any symptoms, but there may have been variation between subjects in thresholds for acknowledging the presence of symptoms, and further difficulty in precisely pinpointing their onset. Some individuals may be more sensitive than others to the effects of GTN on the cardiovascular system, and others compensate more effectively, but neither age nor sex was a predictor of side-effects in this study. In addition, the range of mean plasma concentrations observed following application of a fixed dose of GTN was not sufficiently large to allow satisfactory correlations to be made.

While chemical sphincterotomy with 0·2 per cent GTN is often effective, there is certainly scope for improvement as one-third of patients with chronic anal fissures fail to heal with this treatment, and side-effects are a recognized drawback. Increasing the dose of GTN is likely to increase side-effects, which occur more frequently with higher concentrations of GTN[6,7]. Alternative pharmacological agents to GTN are being evaluated, and topical preparations of the calcium channel blockers diltiazem and nifedipine have been shown to lower RAP significantly, and to heal two-thirds of chronic anal fissures with relatively few side-effects[13,14]. Finally, novel experimental studies using an animal model validated as a model for human IAS[15] have demonstrated that maximal concentrations of GTN (nitric oxide donor) and diltiazem (calcium channel blocker) did not completely abolish IAS tone independently[16]. However, by acting via different pathways, these drugs may produce an additive effect when combined; it is conceivable that a combination treatment may improve efficacy and simultaneously reduce the incidence of side-effects by allowing a lower dose of GTN to be used. Further studies are required to determine the role of combination preparations in the treatment of chronic anal fissure.

Acknowledgements

The authors thank Dr K. R. Neal for statistical advice. Dr M. Jonas was supported by a Royal College of Surgeons of England Research Fellowship.

References

1. Chakder S, Rattan S. Release of nitric oxide by activation of nonadrenergic noncholinergic neurons of internal anal sphincter. *Am J Physiol* 1993; **264:** G7–12.
2. Rattan S, Chakder S. Role of nitric oxide as a mediator of internal anal sphincter relaxation. *Am J Physiol* 1992; **262:** G107–12.
3. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in the treatment of anal fissure. *Lancet* 1997; **349:** 11–14.
4. Kennedy ML, Sowter S, Nguyen H, Lubowski DZ. Glyceryl trinitrate ointment for the treatment of chronic anal fissure: results of a placebo-controlled trial and long-term follow-up. *Dis Colon Rectum* 1999; **42:** 1000–6.
5. Carapeti EA, Kamm MA, McDonald PJ, Chadwick SJ, Melville D, Phillips RK. Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut* 1999; **44:** 727–30.
6. Hyman NH, Cataldo PA. Nitroglycerin ointment for anal fissures: effective treatment or just a headache? *Dis Colon Rectum* 1999; **42:** 383–5.
7. Palazzo FF, Kapur S, Steward M, Cullen PT. Glyceryl trinitrate treatment of chronic fissure *in ano*: one year's experience with 0·5% GTN paste. *J R Coll Surg Edinb* 2000; **45:** 168–70.
8. Lee FW, Watari N, Rigod J, Benet LZ. Simultaneous determination of nitroglycerin and its dinitrate metabolites by capillary gas chromatography with electron-capture detection. *J Chromatogr* 1988; **426:** 259–66.
9. Bogaert MG. Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. *Clin Pharmacokinet* 1987; **12:** 1–11.
10. Guillemot F, Lone YC, Leroi H, Lamblin MD, Cortot A. Nitroglycerin *in situ* reduces upper anal canal pressure. *Dig Dis Sci* 1992; **37:** 155.
11. Loder PB, Kamm MA, Nicholls RJ, Phillips RKS. 'Reversible chemical sphincterotomy' by local application of glyceryl trinitrate. *Br J Surg* 1994; **81:** 1386–9.
12. Jonas M, Wright JW, Neal KR, Scholefield JH. Topical 0·2% glyceryl trinitrate has a short-lived effect on resting anal pressure. *Colorectal Disease* 2000; **2**(Suppl 1): (Abstract).
13. Antropoli C, Perrotti P, Rubino M, Martino A, De Stefano G, Migliore G *et al.* Nifedipine for local use in conservative treatment of anal fissures: preliminary results of a multicenter study. *Dis Colon Rectum* 1999; **42:** 1011–15.
14. Jonas M, Scholefield JH. Oral and topical diltiazem are effective treatment for chronic anal fissures. *Gut* 2000; **46**(Suppl II): A83 (Abstract).
15. Mundey MK, Jonas M, Worthley T, Scholefield JH, Wilson VG. Pharmacological characterization of neurogenic responses of the sheep isolated internal anal sphincter. *Br J Pharmacol* 2000; **130:** 489–94.
16. Jonas M, Wilson VG, Scholefield JH. Comparison of the effects of glyceryl trinitrate (GTN) and diltiazem on isolated sheep internal anal sphincter. *Gut* 2000; **46**(Suppl II): A83 (Abstract).

Original article

Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer

J. Camilleri-Brennan and R. J. C. Steele

University Department of Surgery and Molecular Oncology, Level 6, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
Correspondence to: Mr J. Camilleri-Brennan (e-mail: johncbrennan@doctors.org.uk)

Background: Little is known of how the quality of life of patients with rectal cancer changes after surgery, and whether or not quality of life is associated with and predictive of survival. The aims of this study were to address these issues.

Methods: The Medical Outcomes Study Short Form 36 (SF-36), and the European Organization for the Research and Treatment of Cancer QLQ-C30 and QLQ-CR38 quality of life questionnaires were administered to patients before surgery for rectal cancer, on discharge home and at 3-month intervals after operation for up to 1 year. Survival was measured in days from the time of surgery to death.

Results: Sixty-five patients with a median age of 67 years participated. Most quality of life scores dropped significantly below baseline in the early postoperative period. From the third month onwards some scores, such as the global quality of life score and emotional function score on the QLQ-C30, improved. Other scores, including role function, fatigue and pain on the QLQ-C30, were similar to baseline values after 3–6 months and remained unchanged. However, scores such as sexual enjoyment and male sexual problems on the QLQ-CR38 were worse than baseline in the early postoperative period and remained poor thereafter. Stepwise regression analyses showed that preoperative quality of life dimension scores for physical function, nausea/vomiting and sexual enjoyment, together with age, predicted postoperative 1-year survival with an accuracy of 76·8 per cent.

Conclusion: The findings of this study confirm that quality of life after rectal cancer surgery changes with time. It is generally worst in the early postoperative period. Preoperative quality of life is a good predictor of survival at 1 year.

Paper accepted 9 August 2001

British Journal of Surgery 2001, **88**, 1617–1622

Introduction

Rectal cancer and the consequences of rectal surgery and adjuvant treatment have an important bearing on a patient's quality of life[1]. Quality of life assessment is regarded an important outcome measure in addition to traditional endpoints such as tumour recurrence and survival[2]. However, although quality of life is dynamic, little is known about how the quality of life of patients with rectal cancer changes with time after surgery.

Some studies have shown that quality of life scores may predict survival[3–9]. These studies involved patients who were having chemotherapy or best supportive care for advanced malignant disease. No studies have been done to determine the prognostic significance of preoperative quality of life scores for survival in primary rectal cancer.

This paper describes a prospective analysis of the quality of life of patients with rectal cancer undergoing resection of the primary tumour. The main aim was to determine how the quality of life of patients having surgery for rectal cancer changes with time. A subsidiary aim was to determine to what extent preoperative sociodemographic and clinical variables and quality of life scores predict survival at 1 year after surgery.

Patients and methods

From September 1997 to April 1999, 82 patients with cancer of the rectum or rectosigmoid junction were scheduled for elective rectal resection at Ninewells Hospital, Dundee. The patients were considered to be eligible for the study if they had primary adenocarcinoma of the rectum or rectosigmoid junction that was locally resectable. Patients with locally recurrent cancer, with multifocal colorectal cancer or who suffered from another malignancy were excluded. Three patients were considered

Table 1 Demographic and clinical details of participating patients who had surgery for rectal cancer

Median (range) age (years)	67 (44–84)
Men	45
Women	20
ASA grade	
I	17
II	40
III	8
Deprivation categories	
1 and 2 (affluent)	30
3, 4 and 5	27
6 and 7 (deprived)	8
Dukes' stage of rectal cancer	
A	16
B	14
C	28
'D' (liver metastases)	7
Type of operation	
Anterior resection	21
Anterior resection + ileostomy	26
Abdominoperineal resection	18
Mesorectal excision	
Partial	19
Total	46
Adjuvant treatment	
Preoperative radiotherapy	8
Postoperative radiotherapy	9
Postoperative chemotherapy	26
Cryotherapy of liver metastases	3

ASA, American Society of Anesthesiologists

to be ineligible at this stage. The remaining 79 patients were then contacted and invited to participate in the study. Seventy-two patients agreed to participate, giving their full informed consent. The study was approved by the Tayside Committee on Medical Research Ethics.

Those who accepted were given three quality of life questionnaires in the week before surgery: the European Organization for Research and Treatment of Cancer QLQ-C30[10] and QLQ-CR38[11] and the Medical Outcomes Study Short Form 36 (SF-36)[12]. Seventy patients filled in a baseline questionnaire. Quality of life was also assessed on discharge home (early postoperative assessment), and at 3, 6, 9 and 12 months after operation.

The QLQ-C30[10] is a cancer-specific questionnaire covering a wide range of dimensions that are relevant to any patient with cancer. Levels of functioning in various areas, such as physical and emotional, and symptoms such as pain and fatigue, are assessed. In addition there is a global quality of life scale which is used as the overall summary measure of quality of life. The colorectal cancer module, the QLQ-CR38[11], addresses areas of particular relevance to patients with colorectal cancer, such as gastrointestinal, defaecation and stoma-related problems, sexuality and image. The SF-36[12] is a generic, multidimensional questionnaire that was designed to measure health-related quality of life in various clinical settings and to be applicable across social and demographic groups.

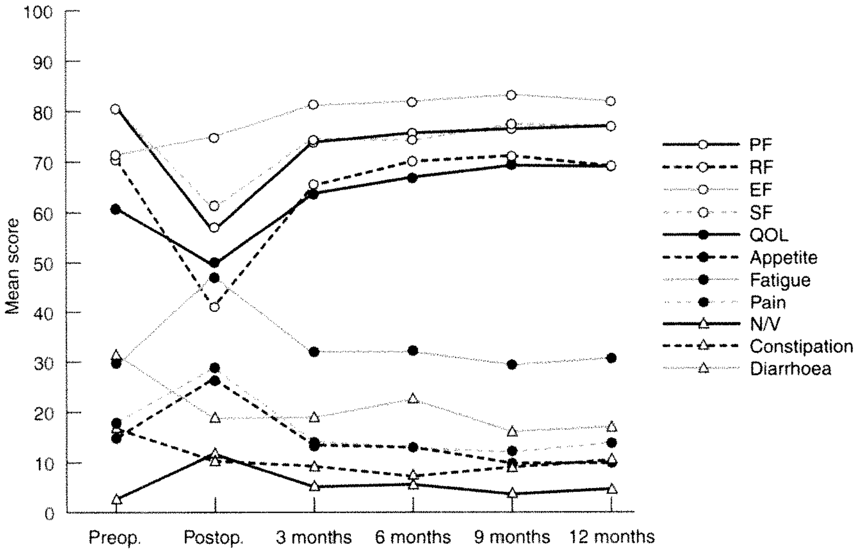


Fig. 1 Quality of life profiles of all patients treated for rectal cancer, QLQ-C30 questionnaire. Values are mean scores. Higher scores for functional scales (physical function (PF), role function (RF), emotional function (EF) and social function (SF)) and global quality of life scale (QOL) represent a higher level of functioning and quality of life, while higher scores for symptom scales (fatigue, nausea and vomiting (N/V), appetite, pain, constipation and diarrhoea) represent a higher level of symptoms. Preop., preoperative; postop., postoperative

Details regarding age, gender, deprivation category (a measure of socioeconomic status based on the postcode)[13], American Society of Anesthesiologists (ASA) score, Dukes' stage of tumour, operation type, and neoadjuvant and adjuvant treatment were collected. The patients were followed up for 1 year. Survival was measured in days from the time of surgery to death.

Statistical analysis

The non-parametric Friedman's two-way analysis of variance test was used to identify any overall significant differences between the scores at different time points for each dimension. When the overall *P* value was significant, a Wilcoxon signed rank test for paired data was used to compare pairs of quality of life scores. Survival curves were estimated by the Kaplan–Meier method, using the log rank test to assess the significance of differences. Kendall's correlation was used to assess correlations between variables. A stepwise regression analysis was used to establish which variables best predicted survival. A 2 per cent level of significance was chosen ($P < 0{\cdot}02$) to reduce the risk of type I errors arising from multiple testing. Statistical analyses were carried out using SPSS version 9.0 (SPSS, Chicago, Illinois, USA).

Results

Of the 70 patients who answered the questionnaires, five were excluded from the study. The total number of eligible participants was thus 65 (*Table 1*). Forty-six patients had rectal excision using the technique of total mesorectal excision[14]. In the other 19 patients partial mesorectal excision with a lower excision margin of at least 5 cm was performed. Eight participants (all men) died during the first year after operation.

General trends in quality of life changes with time

The results are shown in *Fig. 1* (QLQ-C30), *Fig. 2* (QLQ-CR38) and *Fig. 3* (SF-36). In the early postoperative assessment (on discharge home) the scores of most quality of life dimensions were significantly worse than baseline values. By 3–6 months after operation most scores had returned to baseline levels. Some scores, such as global quality of life score and emotional function (QLQ-C30) were significantly better than baseline values. Some areas of quality of life, however, such as sexual enjoyment, male sexual problems and perception of body image (QLQ-CR38) were significantly worse at each postoperative assessment compared with baseline.

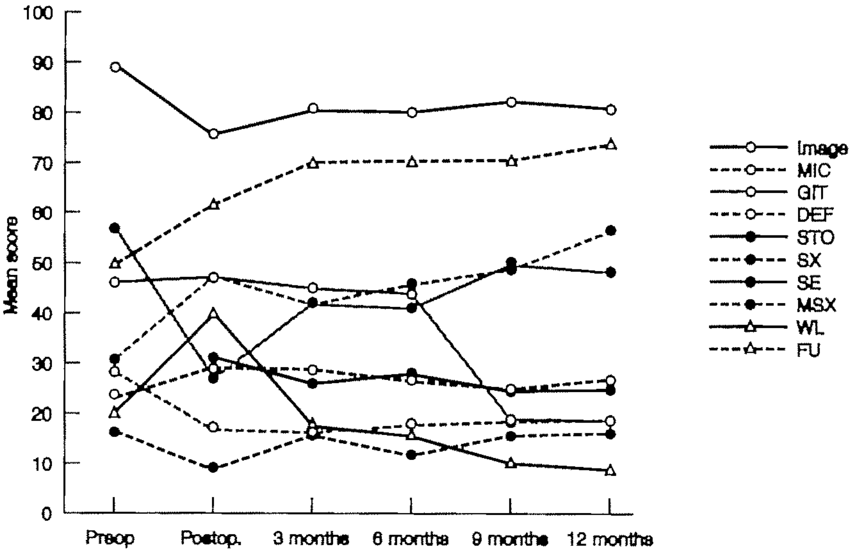


Fig. 2 Quality of life profiles of all patients treated for rectal cancer, QLQ-CR38 questionnaire. Values are mean scores. Higher scores for functional scales (body image perception (image), sexual function (SX), sexual enjoyment (SE) and future perspective (FU)) represent a higher level of functioning, while higher scores for symptom scales (micturition problems (MIC), gastrointestinal tract problems (GIT), defaecation-related problems in patients who had anterior resection without an ileostomy (DEF), stoma-related problems in patients who had an abdominoperineal resection (STO), male sexual problems (MSX) and weight loss (WL)) represent a higher level of symptomatology. Preop., preoperative; postop., postoperative

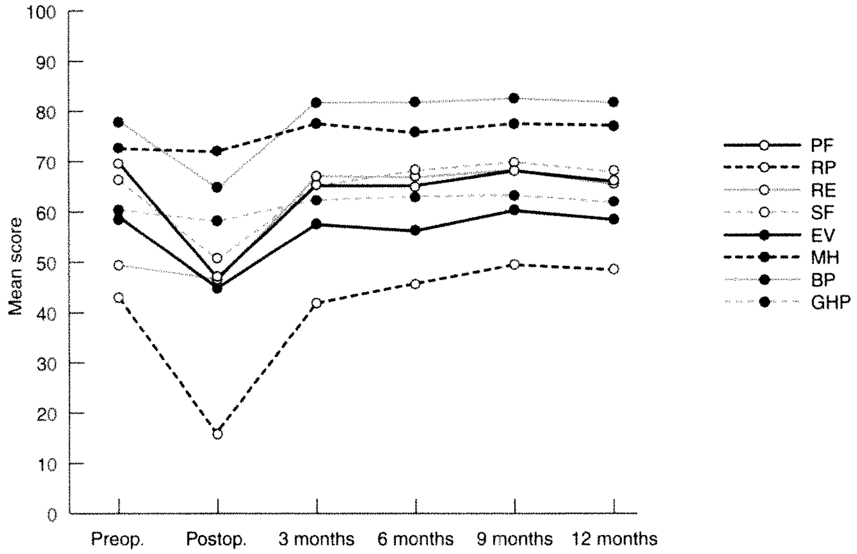


Fig. 3 Quality of life profiles of all patients treated for rectal cancer, Short Form 36 questionnaire. Values are mean scores; the higher the score, the better the quality of life. PF, physical functioning; RP and RE, role limitations because of physical and emotional problems respectively; SF, social functioning; EV, energy and vitality; MH, mental health; BP, body pain; GHP, general health perception; preop., preoperative; postop., postoperative

Correlation with survival

A positive correlation was present between survival and preoperative physical function (PF) (QLQ-C30) (Kendall's coefficient $t = 0{\cdot}37$), PF (SF-36) ($t = 0{\cdot}30$), social function (SF-36) ($t = 0{\cdot}22$), mental health (SF-36) ($t = 0{\cdot}23$) and energy/vitality (SF-36) ($t = 0{\cdot}23$). There was a negative correlation between survival and age ($t = -0{\cdot}27$), preoperative ASA status ($t = -0{\cdot}30$), preoperative fatigue (QLQ-C30) ($t = -0{\cdot}22$) and dyspnoea (QLQ-C30) ($t = -0{\cdot}42$). There was no correlation between Dukes' stage and survival at 1 year.

Prediction of survival

The overall probability of survival at 1 year after elective surgery for primary rectal cancer was 0·88 (95 per cent confidence interval 0·80–0·96). Stepwise multiple regression analysis showed that preoperative ASA score and gender could explain 15·4 per cent of the variation in survival (adjusted $R^2 = 0{\cdot}154$). There was a difference in survival (log rank 3·87, $P = 0{\cdot}049$) between male and female patients. Dukes' stage of tumour was not predictive of survival at 1 year.

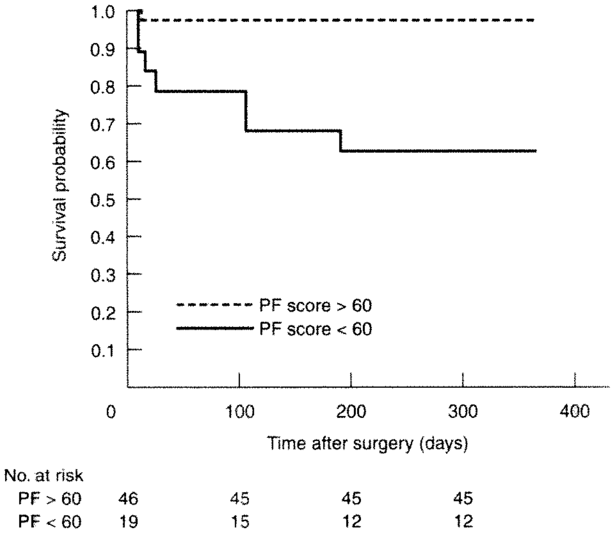


Fig. 4 Kaplan–Meier curves comparing the probability of surviving 1 year after surgery for rectal cancer between patients with a physical function (PF) score of more than 60 and patients with a PF score of 60 or less (log rank 15·5, $P < 0{\cdot}001$)

Stepwise multiple regression analysis was also done using quality of life scores alone as independent variables. The domains of preoperative PF, pain and appetite (all QLQ-C30), and pain (SF-36) could explain 39·4 per cent of the variation in survival (adjusted $R^2 = 0{\cdot}394$). Other quality of life domains did not give a significant contribution. There was a significant difference in survival (log rank 15·5, $P < 0{\cdot}001$) between patients with a preoperative PF (QLQ-C30) score of 60 or less and patients with a score of more than 60 (*Fig. 4*). A patient with a PF score of 60 or less is either housebound or is limited to short walks outside the

Table 2 Model that best predicts 1-year survival after surgery for rectal cancer

Step	Variable	R	R^2	Adjusted R^2
1	Physical function (QLQ-C30)	0·628	0·394	0·361
2	Nausea/vomiting (QLQ-C30)	0·801	0·642	0·599
3	Age	0·857	0·734	0·685
4	Sexual enjoyment (QLQ-CR38)	0·904	0·817	0·768

house. On the other hand, a score of more than 60 represents a good PF, with the patient able to carry out at least moderately strenuous activities such as walking for long distances.

Stepwise multiple regression analysis was repeated using survival as the outcome variable and sociodemographic, clinical and preoperative quality of life variables as independent variables. The results showed that preoperative PF and nausea and vomiting (both QLQ-C30), sexual enjoyment (QLQ-CR38) and age could explain 76·8 per cent of the variation in survival (adjusted $R^2 = 0{\cdot}768$) (*Table 2*).

Discussion

The patients in this study are representative of patients with rectal cancer attending a typical colorectal cancer unit in the UK. Trends for each dimension of quality of life in three questionnaires (QLQ-C30, QLQ-CR38 and SF-36) were studied. In general, the scores of many quality of life dimensions were lower than baseline in the early postoperative period. This was expected, especially in those dimensions that assessed physical performance such as physical function, role-physical and fatigue. Patients were in the convalescent period of major surgery, and they were also slowly adjusting themselves to a stoma (colostomy or ileostomy) or to a neorectum. Surgery also restricted the social life of these patients for the first few months. By 3–6 months most scores had returned to baseline (preoperative) values. The scores of most dimensions then remained similar to baseline, although some, such as the global quality of life score and emotional function, improved with time. On the other hand, other scores, including perception of body image, were worse than baseline for the whole year after operation. Poor perception of body image may have resulted from the difficulty in accepting a stoma or abdominal scars[15], although improved emotional function, mental health and future perspective reflect a positive and optimistic attitude despite disfiguring surgery.

There was a gradual return to normal bowel function over a period of 1 year, with diarrhoea being significantly improved at 9 and 12 months. Gastrointestinal problems, such as abdominal pain and bloatedness, improved from the third month onwards. Defaecation-related problems in patients who had a high anterior resection improved significantly with time, consistent with other results reported in the literature for this group of patients[1]. Patients with a permanent colostomy experienced a slight but non-significant improvement in stoma-related problems with time. Sexual function and sexual enjoyment deteriorated in the postoperative period and the latter remained poor over the year of assessment. Male sexual problems were likewise increased. Micturition problems also increased after operation, but improved to preoperative levels by 6 months. Sexual and urological problems usually occur because of damage sustained to the pelvic autonomic nerves and pelvic floor during dissection of the rectum[16], although attempts were made to minimize this by using the technique of total mesorectal excision and nerve preservation described by Heald and Ryall[14]. Pelvic radiotherapy may also have a detrimental effect[17,18]. However, part of the problem of postoperative sexual dysfunction may be psychological[15], and related to increasing age[19].

Quality of life scores have been shown to be predictors of survival in patients with advanced disease having palliative treatment[3–9]. However, the present study is the first to demonstrate the prognostic significance of preoperative quality of life scores for survival in primary rectal cancer. The combination of sociodemographic and clinical variables with quality of life scores gave a model that could predict 1-year survival with an accuracy of 76·8 per cent. Earlam and colleagues[7] similarly derived a model with an accuracy of 74 per cent for predicting survival, but in patients with advanced colorectal disease undergoing chemotherapy. Preoperative PF on the QLQ-C30 was a particularly important predictor of survival, and patients with a PF score of more than 60 had a significantly better survival than those with lower scores. Sexual enjoyment scores were also predictive of survival. High sexual enjoyment scores were associated with a younger age group and a good PF. On the other hand, preoperative nausea and vomiting and appetite loss conferred a survival disadvantage. These symptoms could indicate early bowel obstruction caused by the rectal cancer, which could have been a contributory factor in patients' deaths. It is of interest that, in the short term, these quality of life factors were more important than tumour staging in predicting survival. This observation is almost certainly related to duration of follow-up, but highlights the potential usefulness of quality of life assessments.

This study has demonstrated clearly that the quality of life of patients with rectal cancer is dynamic. Studies in other areas of surgical oncology, such as following resection of oesophageal carcinoma[20] and gastric cancer[21], support the importance of longitudinal assessment of quality of life. The measurement of the quality of life of individual patients is seldom done at present as part of routine surgical practice[22], but this should change. Quality of life measurement may help to identify those areas, before and after surgery, that may have been affected by the disease or by its treatment so that intervention may be directed towards improving specific areas of quality of life. In addition, assessment of quality of life gives valuable prognostic information, not only in patients with advanced disease but also in patients with mainly primary disease treated actively in a routine hospital setting. The availability of such information may help the surgeon when obtaining informed consent from patients before major surgery for rectal cancer.

Acknowledgements

The authors thank Dr S. Ogston for advice on statistical analysis, and ConvaTec and Tenovus (Scotland) for financial support of the study.

References

1 Camilleri-Brennan J, Steele RJC. Quality of life after treatment of rectal cancer. *Br J Surg* 1998; **85:** 1036–43.

2 Olschewski M, Schulgen G, Schumacher M, Altman DG. Quality of life assessment in clinical cancer research. *Br J Cancer* 1994; **70:** 1–5.

3 Kaasa S, Mastekaasa A, Lund E. Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patients' subjective experience of disease and psychosocial well-being. *Radiother Oncol* 1989; **15:** 235–42.

4 Ganz PA, Lee JJ, Siau J. Quality of life assessment. An independent prognostic variable for survival in lung cancer. *Cancer* 1991; **67:** 3131–5.

5 Coates A, Gebski V, Signorini D, Murray P, McNeil D, Byrne M *et al.* Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992; **10:** 1833–8.

6 Coates A, Thomson D, McLeod GR, Hersey P, Gill PG, Olver IN *et al.* Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. *Eur J Cancer* 1993; **29A:** 1731–4.

7 Earlam S, Glover C, Fordy C, Burke D, Allen-Mersh TG. Relation between tumor size, quality of life and survival in patients with colorectal liver metastases. *J Clin Oncol* 1996; **14:** 171–5.

8 Wisløff F, Hjorth M. Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. *Br J Haematol* 1997; **97:** 29–37.

9 Coates A, Porzsolt F, Osoba D. Quality of life in oncology practice: prognostic value of EORTC QLQ-C30 scores in patients with advanced malignancy. *Eur J Cancer* 1997; **33:** 1025–30.

10 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

11 Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *Eur J Cancer* 1999; **35:** 238–47.

12 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF36) 1: conceptual framework and item selection. *Med Care* 1992; **30:** 473–83.

13 Carstairs V, Morris R. *Deprivation and Health in Scotland.* Aberdeen: Aberdeen University Press, 1991.

14 Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **i:** 1479–82.

15 White CA, Hunt JC. Psychological factors in postoperative adjustment to stoma surgery. *Ann R Coll Surg Engl* 1997; **79:** 3–7.

16 Mundy AR. An anatomical explanation for bladder dysfunction following rectal and uterine surgery. *Br J Urol* 1982; **54:** 501–4.

17 Holm T, Singnomklao T, Rutqvist L-E, Cedermark B. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. *Cancer* 1996; **78:** 968–76.

18 Mak AC, Rich TA, Schultheiss TE, Kavanagh B, Ota DM, Romsdahl MM. Late complications of postoperative radiation therapy for cancer of the rectum and rectosigmoid. *Int J Radiat Oncol Biol Phys* 1994; **28:** 597–603.

19 Enker WE. Potency, cure, and local control in the operative treatment of rectal cancer. *Arch Surg* 1992; **127:** 1396–402.

20 Zieren HU, Jacobi CA, Zieren J, Muller JM. Quality of life following resection of oesophageal carcinoma. *Br J Surg* 1996; **83:** 1772–5.

21 Svedlund J, Sullivan M, Liedman B, Lundell L, Sjödin I. Quality of life after gastrectomy for gastric carcinoma: a controlled study of reconstructive procedures. *World J Surg* 1997; **21:** 422–33.

22 Camilleri-Brennan J, Steele RJC. Measurement of quality of life in surgery. *J R Coll Surg Edinb* 1999; **44:** 252–9.

Original article

Function of a colonic J pouch continues to improve with time

G. J. C. Harris, I. C. Lavery and V. W. Fazio

Department of Colorectal Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio, USA
Correspondence to: Mr G. J. C. Harris, Department of General Surgery, 1st Floor North Wing, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK (e-mail: mrguyharris@aol.com)

Background: J pouch–anal anastomosis is thought to give superior functional results to straight coloanal anastomosis after rectal resection. Follow-up studies have suggested that this improvement is not maintained and that evacuatory difficulties may increase.

Methods: Some 119 consecutive patients had a coloanal anastomosis after resection for rectal carcinoma over 113 months, 62 with a J pouch and 57 with a straight coloanal anastomosis. Functional results were determined by patient questionnaire. The two groups were compared for the first and second 5-year intervals of study.

Results: Patients who had a J pouch had significantly better median Kirwan continence scores for the duration of the study and 5–9 years after surgery: 1 *versus* 2 ($P = 0{\cdot}05$) and 1 *versus* 2 ($P < 0{\cdot}01$), respectively. Some 5–9 years after surgery the median number of nocturnal bowel movements was significantly lower in patients who had a J pouch than in those with a straight coloanal anastomosis (0 *versus* 1; $P = 0{\cdot}02$). Similarly, significantly better results were seen with regard to evacuation difficulties and urgency of defaecation.

Conclusion: The function of the J pouch was superior to that of the straight coloanal anastomosis and appeared to improve with time.

Paper accepted 14 August 2001

British Journal of Surgery 2001, 88, 1623–1627

Introduction

In 1972, Parks[1] first described transanal coloanal anastomosis to maintain large bowel continuity after low anterior resection. It was soon recognized that 'anterior resection syndrome', a group of symptoms comprising defaecatory frequency, urgency and soiling, was common afterwards[2]. The condition was thought to be due to the reduced size of the neorectal reservoir. In an attempt to remedy this, the J pouch with coloanal anastomosis was introduced by Lazorthes *et al.*[3] and by Parc *et al.*[4] in 1986. It has been demonstrated in several trials that the functional outcome after construction of a colonic J pouch is superior to that after straight coloanal anastomosis, at least for the first 2 years after surgery[5–9]. It is unclear whether these benefits are maintained in the long term, or whether the evacuation difficulties associated with J pouches increase with time[10,11].

The present study evaluated data from long-term follow-up of patients with a coloanal anastomosis after colorectal cancer.

Patients and methods

Patients who had a coloanal anastomosis after resection of a rectal adenocarcinoma were identified from the colorectal cancer database of the Cleveland Clinic Foundation. All operations were performed by a group practice of similarly trained surgeons in a single institution between February 1990 and June 1999 inclusive. February 1990 was the month in which the first J pouch–anal anastomosis was performed at this institution.

A questionnaire was mailed to all surviving patients. They were asked to give details of their bowel function regarding bowel frequency (day and night), incontinence (to gas, liquids and solids), urgency, use of pads, use of medication to control bowel function and difficulty with evacuation. Any patient who did not return a postal questionnaire was contacted by telephone. A thorough chart review was undertaken and the patients were grouped according to procedure type: J pouch or straight coloanal anastomosis.

Continence was quantified for each patient using the Kirwan score (grade 1, full continence to flatus, liquid and solid stool; grade 2, incontinence to flatus; grade 3, incontinence to flatus and liquids with occasional soiling; grade 4, incontinence to flatus, liquid and solid stools with regular soiling).

Qualitative measurements of urgency, pad use, antidiarrhoea medication and laxative use, incomplete evacuation and need to try more than once to evacuate were scored according to their occurrence: always, occasionally or never.

Symptoms were compared between the two groups, J pouch and straight coloanal anastomosis, for the entire duration of the study, and for each group in the first and second 5-year intervals after surgery. Kirwan scores were also compared in each group by yearly interval. Statistical analysis was made using the Mann–Whitney *U* test for non-parametric data. χ^2 analysis was used for symptom comparison between the two groups.

Surgical technique

Standard oral and mechanical bowel preparation was given before surgery. A midline incision was made and the colon was mobilized from the pelvic brim proximally to the middle colic vessels, which were preserved. A high ligation was then made of the inferior mesenteric vessels. The pelvis was entered using electrocautery in the plane between Waldeyer's fascia and the investing fascia propria of the rectum, and continued to the pelvic floor. The distal rectum was then divided at the level of the sphincters (above a row of staples made with a linear stapler if a double-stapled anastomosis was to be made) after a rectal washout with 40 per cent alcohol. If a pouch was to be fashioned, a linear cutting stapler was used to make a J pouch either 6 or 10 cm in length. Initially a 10-cm pouch was chosen for J pouch construction, but after data pertaining to evacuation difficulties had been published a smaller 6-cm pouch was adopted. The tip of the 'J' was similarly closed with the linear cutting stapler. A coloanal anastomosis was fashioned either with a transanal handsewn or circular stapled technique, depending on the requirement for anal mucosectomy. When a stapled anastomosis was performed, the anastomotic line was 1·5–2·0 cm from the dentate line either at, or just within, the levator complex. For handsewn anastomoses, the suture line was more distal, at the level of the dentate line, well within the levator complex. Anastomotic integrity was checked by filling the pelvis with saline and insufflating the neorectum with air. Proximal diversion by ileostomy was included at the discretion of the surgeon.

Patients received adjuvant chemotherapy or radiotherapy at the discretion of the surgeon and attending oncologist. The type and timing of such adjuvant therapy was recorded from patient charts.

Results

A total of 208 patients was identified who had a straight or J pouch coloanal anastomosis performed for rectal adenocarcinoma between February 1990 and June 1999 inclusive. Over the same interval a further 550 patients were treated for rectal adenocarcinoma (302 anterior resection, 203 abdominoperineal resection, 16 proctectomy and ileal pouch–anal anastomosis, 16 Hartmann's procedure and 13 'coloplasty' pouch–anal anastomosis).

At the time of data collection, 158 patients (76 per cent) with a J pouch or straight anastomosis were still alive; 50 patients had died. Some 39 surviving patients (25 per cent) were excluded from the study: 25 were lost to follow-up, six patients declined to participate, one patient was physically unable because of a recent stroke and seven patients still had a diverting stoma in place.

Of the 119 patients with full follow-up and a functioning anastomosis, 62 patients had a J pouch and 57 had a straight coloanal anastomosis. Seventy-three patients in this group were alive 0–4 years after surgery (48 J pouch and 25 straight anastomosis) and 46 were still alive 5–9 years after surgery (14 J pouch and 32 straight anastomosis). Of the patients who had a J pouch, there were 39 men and 23 women with a mean age of 59 (range 22–81) years. Of the patients who had a straight coloanal anastomosis, there were 43 men and 14 women with a mean age of 60 (range 37–80) years. There was no significant difference between the groups in age or sex. Median follow-up for the whole group was 47 (range 4–117) months, 34 (range 4–117) months after J pouch and 63 (range 9–112) months after straight anastomosis.

Thirty-three patients (53 per cent) with a J pouc anastomosis received adjuvant radiotherapy compared wit 18 (32 per cent) in the straight anastomosis grou (*P* = 0·02). Of the patients with a J pouch, 23 receive preoperative and ten postoperative radiotherapy. Of thos with a straight coloanal anastomosis, six received preopera tive and 12 postoperative radiotherapy; this difference wa significant (*P* = 0·01).

Local tumour recurrence occurred in six (5 per cent) o 119 patients in the study, all after straight coloana anastomosis.

Postoperative bowel function

When patients in all postoperative years were compared b procedure, bowel function was similar. The media frequency of bowel movement in the daytime was 2 i each group; at night-time it was zero in the J pouch group compared with 1 in patients with a straight anastomosis. The median number of bowel movements over 24 h was 2 in each group.

Continence was better in patients with a J pouch; the median Kirwan continence score was 1 compared with 2 for straight coloanal anastomosis ($P = 0·05$).

There was no significant difference between J pouch and straight anastomosis groups for urgency, pad use or use of antidiarrhoeal medication, nor for use of laxatives, feelings of incomplete evacuation or in need to try more than once to open the bowels fully.

Long-term outcome

When J pouch and straight coloanal anastomoses were compared according to the interval after operation, J pouch coloanal anastomoses appeared to function better after 5–9 years (*Table 1*).

There was no significant difference in the median number of bowel movements between J pouch and straight coloanal anastomosis during the day (2 in each group), at night (1 in each group) or over 24 h (3 *versus* 2) in the first 5 years. There was a significant improvement in bowel frequency at night after J pouch construction compared with straight coloanal anastomosis in the second 5-year interval for night (0 *versus* 1; $P = 0·02$) but not for median number of daytime (2 in each group) or total (3 in each group) daily bowel movements.

There was no significant difference in median Kirwan scores between J pouch and straight coloanal anastomosis in the first 5-year interval. However, in the second 5 years the continence score for the J pouch group was significantly better (1 *versus* 2; $P < 0·01$) (*Table 1*).

There was no difference in laxative use between J pouch and straight anastomosis groups in either the first or second 5 years. In the first 5 years of study there was no significant difference between the groups for perceived incomplete evacuation or the need to attempt more than once to open the bowels successfully. In the second 5 years, however, the difference between the groups became significant for both symptoms, favouring the J pouch group ($P = 0·03$ in each case) (*Table 2*).

There was no significant difference between J pouch and straight coloanal anastomosis groups in the first 5 years in the symptoms of urgency to defaecate, or use of pads or antidiarrhoeal medication. However, when patients were compared more than 5 years after surgery, both the urge to defaecate and pad use were significantly better after J pouch anastomosis ($P = 0·02$ and $P = 0·03$ respectively) (*Table 2*).

Table 1 Bowel function by coloanal anastomosis and time after procedure

	0–4 years			5–9 years		
	J pouch	Straight	P^*	J pouch	Straight	P^*
Median no. of bowel movements						
Total 24 h	3	2	n.s.	3	3	n.s.
Day	2	2	n.s.	2	2	n.s.
Night	1	1	n.s.	0	1	0·02
Median Kirwan score	2	2	n.s.	1	2	< 0·01

n.s., Not significant. *Mann–Whitney *U* test

Table 2 Comparison of bowel function after coloanal anastomosis at 5–9 years: 14 patients after J pouch and 32 after straight coloanal anastomosis

	Never	Occasionally	Always	P^*
Laxative use				n.s.
J pouch	10	2	2	
Straight	25	3	4	
More than one try				0·03
J pouch	8	6	0	
Straight	8	14	9	
Incomplete evacuation				0·03
J pouch	1	11	2	
Straight	4	11	16	
Urgency				0·02
J pouch	5	N/A	9	
Straight	22	N/A	9	
Use of pads				0·03
J pouch	11	1	2	
Straight	12	2	18	
Antidiarrhoea medication				n.s.
J pouch	11	1	2	
Straight	14	9	9	

n.s., Not significant; N/A, not applicable. *χ^2 test

Discussion

Since 1990 coloanal anastomoses have been performed by similarly trained departmental staff surgeons using a standard technique of dissection and resection but different methods of anastomosis. The majority of procedures were performed by one of two senior surgeons. One performed a J pouch as a preference in all cases where technically possible, whereas the other performed a straight coloanal anastomosis. The policy of preoperative radiotherapy also varied between the surgeons. These factors explain the similar age and sex mix but difference between groups in the proportion of patients who received adjuvant radiotherapy.

Other studies have shown significant differences between J pouch and straight coloanal anastomosis in the debilitating symptoms of anterior resection syndrome[12,13]. It is stated that frequency of defaecation and continence are improved by the use of a colonic pouch, particularly in the first 1–2 years after surgery[5–9], although symptoms of faecal urgency are often more difficult to ease[14].

In this study, when considering all patients studied for up to 10 years after surgery, there was a significant difference in continence scores favouring the J pouch, in agreement with other studies[12]. However, there was no difference in the frequency of daily defaecation. Nor was there a significant improvement in the troublesome symptom of urgency of evacuation after J pouch anastomosis[7,14].

When the groups were further divided according to the number of years after surgery, there was no difference in the daily frequency of defaecation between the two types of anastomosis 1–4 years after operation. In patients studied after 5–9 years the mean daily frequency of defaecation was lower after J pouch anastomosis; this difference, however, was statistically significant only for the frequency of nocturnal defaecation. Assessment of a larger number of patients might confirm a statistical significance in the day as well.

Overall Kirwan continence scores were better after J pouch anastomosis and appeared to improve at a greater rate than those in patients with a straight anastomosis (*Table 1*). In the patients studied 5–9 years after operation the difference in continence scores became significant. The symptom of perceived urgent need to defaecate appeared to improve with time. In the later interval the difference between J pouch and straight anastomosis became significant, favouring the pouch. Other authors report that this symptom, which is part of the anterior resection syndrome, was not improved by a reservoir procedure. The improvement in urgency to evacuate that increases with time may be the result of continued pouch dilatation.

No significant difference between the operative groups was identified over all years of the study for any of the following factors: need to use pads, requirement for antidiarrhoeal or laxative medication, feeling of incomplete evacuation or need to try more than once to defaecate.

It has been suggested that split defaecation[11] is a problem with a J pouch and that difficulty with pouch evacuation increases with time owing to progressive dilatation[10]. Construction of a smaller pouch (5–6 cm) and avoidance of a long rectal stump decreases the incidence of this evacuation difficulty[15,16]. In the present study there was no significant difference in perceived incomplete evacuation or the need to attempt more than once to defaecate in the patients studied 0–4 years after surgery. In contrast there was a significant difference in both factors 5–9 years after surgery, favouring the J pouch, even though this group had a greater proportion of the larger 10-cm J pouches.

Wexner and Alabaz[17] in their review article also concluded that a colonic J pouch is associated with significantly better bowel function and less evacuatory difficulty than a straight coloanal anastomosis. The present study suggests that the superior function of a J pouch continues beyond the 1–2 years[5,13] usually cited as the time at which the two procedures become functionally equivalent.

Several authors have suggested that radiation to soft tissues of the pelvis worsens postoperative neorectal reservoir function[18], particularly if the treatment is administered after operation. In the present study patients with a J pouch were more likely to receive irradiation and yet had overall better function than those with a straight coloanal anastomosis. If patients who received adjuvant radiotherapy were excluded from analysis the frequency of defaecation was almost identical to that of patients as a whole (four in each group).

These data suggest that the construction of a J-pouch after rectal resection and coloanal anastomosis confers benefit to the patient in terms of improved continence scores compared with those achieved with a straight anastomosis. They also suggest that continence scores, nocturnal defaecatory frequency, urgency and pouch evacuation difficulties may continue to improve as the time interval after surgery increases.

References

1 Parks AG. Transanal technique in low rectal anastomosis. *Proc R Soc Med* 1972; **65:** 975–6.

2 Ortiz H, Armendariz P. Anterior resection: do the patients perceive any clinical benefit? *Int J Colorectal Dis* 1996; **11:** 191–5.

3 Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. *Br J Surg* 1986; **73:** 136–8.

4 Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. *Br J Surg* 1986; **73:** 139–41.

5 Joo JS, Latulippe JF, Alabaz O, Weiss EG, Nogueras JJ, Wexner SD. Long-term functional evaluation of straight coloanal anastomosis and colonic J-pouch: is the functional superiority of the colonic J-pouch sustained? *Dis Colon Rectum* 1998; **41:** 740–6.

6 Lazorthes F, Chiotasso P, Gamagami RA, Istvan G, Chevreau P. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. *Br J Surg* 1997; **84:** 1449–51.

7 Ho YH, Tan M, Seow-Choen F. Prospective randomized

controlled study of clinical function and anorectal physiology after low anterior resection: comparison of straight and colonic J pouch anastomoses. *Br J Surg* 1996; **83**: 978–80.

8 Kusonoki M, Shoji Y, Yanagi H, Hatada T, Fujita S, Sakanoue Y *et al.* Function after anoabdominal rectal resection and colonic J pouch anal anastomosis. *Br J Surg* 1991; **78**: 1434–8.

9 Berger A, Tiret E, Parc R, Frileux P, Hannoun L, Nordlinger B *et al.* Excision of the rectum with colonic J pouch–anal anastomosis for adenocarcinoma of the low and mid rectum. *World J Surg* 1992; **16**: 470–7.

10 Hida J, Yasutomi M, Maruyama T, Tokoro T, Wakano T, Uchida T. Enlargement of colonic pouch after proctectomy and coloanal anastomosis: potential cause for evacuation difficulty. *Dis Colon Rectum* 1999; **42**: 1181–8.

11 Pelissier EP, Blum D, Bachour A, Bosset JF. Functional results of coloanal anastomosis with reservoir. *Dis Colon Rectum* 1992; **35**: 843–6.

12 Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. *Ann Surg* 1996; **224**: 58–65.

13 Seow-Choen F, Goh HS. Prospective randomized trial comparing J colonic pouch–anal anastomosis and straight coloanal reconstruction. *Br J Surg* 1995; **82**: 608–10.

14 Dennett ER, Parry BR. Misconceptions about the colonic J pouch: what the accumulating data show. *Dis Colon Rectum* 1999; **42**: 804–11.

15 Lazorthes F, Gamagami R, Chiotasso P, Istvan G, Muhammad S. Prospective, randomized study comparing clinical results between small and large colonic J-pouch following coloanal anastomosis. *Dis Colon Rectum* 1997; **40**: 1409–13.

16 Hida J, Yasutomi M, Maruyama T, Fujimoto K, Nakajima A, Uchida T *et al.* Indications for colonic J-pouch reconstruction after anterior resection for rectal cancer: determining the optimum level of anastomosis. *Dis Colon Rectum* 1998; **41**: 558–63.

17 Wexner SD, Alabaz O. Anastomotic integrity and function: role of the colonic J-pouch. *Semin Surg Oncol* 1998; **15**: 91–100.

18 Dehni N, Tiret E, Singland JD, Cunningham C, Schlegel RD, Guiguet M *et al.* Long-term functional outcome after low anterior resection: comparison of low rectal anastomosis and colonic J-pouch–anal anastomosis. *Dis Colon Rectum* 1998; **41**: 817–23.

Original article **BJS Research Bursary Winner**

Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer

M. L. George*†, A. S. K. Dzik-Jurasz‡, A. R. Padhani‡, G. Brown§, D. M. Tait¶, S. A. Eccles† and R. I. Swift*

*Department of Surgery, Mayday University Hospital, Thornton Heath, †Section of Cancer Therapeutics, Institute of Cancer Research, and ‡Cancer Research Campaign Clinical Magnetic Resonance Research Group, §Academic Department of Diagnostic Radiology and ¶Department of Gastrointestinal Oncology, Royal Marsden NHS Trust, Sutton, UK

Correspondence to: Mr M. L. George, McElwain Laboratories, Institute of Cancer Research, 15 Cotswold Road, Belmont, Sutton SM2 5NG, UK (e-mail: m.l.george@btinternet.com)

Background: Tumour neoangiogenesis can be assessed non-invasively by measuring angiogenic cytokine concentrations in peripheral circulation and by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). The aim of this study was to assess whether these methods can predict and monitor response to treatment in patients with rectal cancer treated with preoperative chemoradiotherapy.

Methods: Serum and plasma vascular endothelial growth factor levels were measured in 31 patients with T_3/T_4 rectal cancers before quantitating tumour permeability (ln K^{trans}) by DCE-MRI. Sixteen patients receiving preoperative chemoradiotherapy had serial vascular endothelial growth factor (VEGF) and DCE-MRI measurements. Response to treatment was assessed using World Health Organization criteria.

Results: Serum VEGF and ln K^{trans} correlated before treatment ($r = 0{\cdot}48$, $P = 0{\cdot}01$). Responsive tumours ($n = 8$) had higher pretreatment permeability values than non-responsive tumours ($n = 8$) (mean ln K^{trans} $-0{\cdot}46$ and $-0{\cdot}72$ respectively; $P = 0{\cdot}03$). Compared with pretreatment values, responsive tumours showed a marked reduction in permeability at the end of treatment (mean ln K^{trans} $-0{\cdot}46$ and $-0{\cdot}86$ respectively; $P = 0{\cdot}04$). Pretreatment serum VEGF levels were not statistically different between the two groups.

Conclusion: Rectal tumours with higher permeability at presentation appear to respond better to chemoradiotherapy than those of lower permeability. This may allow preselection of appropriate tumours for these regimens, with patients with low-permeability tumours being considered for alternative therapies.

Paper accepted 22 August 2001

British Journal of Surgery 2001, **88**, 1628–1636

Introduction

Angiogenesis, the development of new blood vessels, is required for tumours to grow larger than 2–3 mm^3 in size[1], and provides both nutrients and access to the systemic circulation with possible subsequent metastasis. This angiogenic process is mediated by several potent peptides, which include fibroblast growth factors and vascular endothelial growth factors (VEGFs); VEGF-A is probably the key regulator of angiogenesis. VEGF-A, also known as vascular permeability factor, has potent mitogenic and vascular permeability-enhancing activities specific for endothelial cells, and is synthesized and secreted by both tumour and host cells.

Current methods of assessing tumour angiogenesis may be considered as either direct or indirect. The most frequently used direct methods are microvessel density counts, immunostaining and reverse transcription polymerase chain reaction (RT-PCR) for angiogenic cytokines. All of these techniques require tumour tissue and are therefore generally performed on postoperative specimens.

More recently, measurement of indirect or 'surrogate' markers of angiogenesis, such as blood levels of angiogenic

---

The Editors have satisfied themselves that all authors have contributed significantly to this publication

factors, and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) have been used. Advantages of these indirect methods are that they are non-invasive, can be performed *in situ* rather than on postoperative specimens, and may be used to monitor response to treatment. Both techniques are quantitative and, in the case of DCE-MRI, the functional status of the vasculature can be assessed, whereas microvessel counting provides anatomical data only[2]. However, it is not clear whether levels of angiogenic cytokines within the tumour are mirrored by levels in the peripheral circulation[3].

Serum and plasma levels of VEGF have been shown to correlate with preoperative disease stage in colorectal cancer[4]. This relationship may prove useful in monitoring response and downstaging of locally advanced rectal cancers treated with preoperative chemoradiotherapy, and in the follow-up of patients with resected tumours. However, no longitudinal studies have been reported to date.

The aim of this study was to assess whether indirect measures of angiogenesis could be used to predict and assess response to treatment in colorectal cancer. Initially the relationship between circulating VEGF levels and tumour VEGF levels was studied. DCE-MRI estimates of tumour vascular permeability were then compared with circulating VEGF levels. Finally, changes in serum VEGF and DCE-MRI tumour permeability during chemoradiotherapy in patients with T_3/T_4 rectal cancer, and changes in circulating VEGF levels during the follow-up of patients after primary tumour resection, were measured.

Patients and methods

Patients and treatment

Consecutive patients with colorectal cancer were recruited from the Mayday University Hospital and the Royal Marsden Hospital National Health Service Trust between October 1998 and September 2000. Scientific and ethics committee approval was obtained from both hospitals. Initially only plasma samples were obtained, but later both serum and plasma samples were taken. The majority of tumour samples were obtained after surgical resection (Mayday University Hospital). Patients referred to the Royal Marsden Hospital for consideration of preoperative chemoradiotherapy or palliative chemotherapy were recruited for DCE-MRI studies.

Tumour and circulating vascular endothelial growth factor levels

Serum and plasma samples were obtained before surgical resection from 57 patients, who did not receive preoperative chemoradiotherapy, and assayed for VEGF. A platelet count was also performed so that the serum VEGF level could be calculated relative to platelet count as described previously[4].

Tumour tissue was taken from the surgically resected specimens of these 57 patients and snap frozen in liquid nitrogen until analysis. Messenger RNA (mRNA) expression of tumour VEGF was measured using semiquantitative RT-PCR.

Follow-up study

Serum and plasma VEGF levels from 52 patients found to have no evidence of recurrent disease at the time of surveillance colonoscopy (12 months after surgery) and from 18 patients with recurrent or progressive disease were also measured. These were compared with VEGF levels at the time of diagnosis to assess changes in VEGF during follow-up. No patient had received preoperative chemoradiotherapy.

Dynamic contrast-enhanced magnetic resonance imaging and circulating vascular endothelial growth factor levels in patients with rectal cancer

Thirty-one patients, 23 with T_3/T_4 rectal cancers and eight with an unresected primary rectal cancer (T_3/T_4) and liver metastases, underwent DCE-MRI with serum ($n = 28$) and plasma ($n = 31$) VEGF samples being taken for analysis immediately before MRI. Of these 31 patients, 16 underwent preoperative chemoradiotherapy, with DCE-MRI performed 10–12 weeks after commencing chemotherapy and 3–6 weeks after completing chemoradiotherapy. Two other patients received chemoradiotherapy but did not undergo DCE-MRI (one because of a coronary stent and the other owing to the presence of internal surgical clips). Blood samples for VEGF were taken on average every 3–4 weeks during chemotherapy and every 2 weeks during chemoradiotherapy.

Chemoradiotherapy

Patients were selected for chemoradiotherapy if there was concern about adequate surgical clearance (seven patients had tumour extension to the mesorectal fascial plane and two had extension to within 1 mm as assessed by MRI). Three patients had undergone laparotomy and were found to have irresectable tumours (all T_4). In one male patient an anterior T_3 tumour (on MRI) was clinically fixed. Four patients had bulky T_3 tumours with N_2 disease and one patient had a T_4 tumour with a solitary liver metastasis. The regimen chosen was an extension of the experience obtained with combination chemotherapy in advanced colorectal disease from a previous randomized trial[5], and was part of an ongoing clinical trial. In total 18 patients underwent chemoradiotherapy treatment with protracted venous infusion of 5-fluorouracil (5-FU) 300 mg per m^2 per day delivered via a Hickman line for 12 weeks. Mitomycin C 7 mg/m^2 was administered at the start of treatment and at 6 weeks. After 12 weeks, chemoradiotherapy was undertaken for 6 weeks during which the 5-FU continued at a reduced dose of 200 mg per m^2 per day. Radiotherapy was delivered in two phases using a computed tomography (CT) -planned, conformally blocked, three-field technique. Phase I delivered 25 fractions of 1·8 Gy to a total of 45 Gy; the aim of phase II was to deliver a boost to the tumour of 9 Gy in five fractions. Surgery was undertaken in 15 patients, 4–10 (median 6) weeks after the completion of radiotherapy.

Methods

Measurement of serum and plasma vascular endothelial growth factor levels

Blood was taken into a citrate tube for plasma analysis, and serum separator tubes or clot activator tubes for serum analysis. Samples were centifuged at 1400*g* for 10 min within 30 min of collection. The samples were stored at –70°C until assay by enzyme-linked immunosorbent assay (ELISA) (VEGF ELISA; R & D systems, Oxford, UK). The limits of sensitivity of the ELISA were 9 and 2000 pg/ml. All samples were measured in duplicate.

Reverse transcriptase polymerase chain reaction

Total RNA was extracted from 57 tumour samples and VEGF-A mRNA expression was measured using RT-PCR as described previously[6]. The intensity of the PCR products was semiquantified with the intensity of their respective β-actin bands, and was expressed as arbitrary units.

Magnetic resonance imaging

MRI was carried out using a 1·5-T clinical Siemens Vision system (Siemens Medical Systems, Erlangen, Germany). A four-element pelvic phased-array coil was used to acquire the imaging data. All patients received gadopentate dimeglumine 0·2 mmol/kg (Schering Healthcare, Burgess Hill, UK) intravenously through a peripheral line at 5 ml/s using a power injector (Medrad, Maastricht, The Netherlands).

Axial T2 images (repetition time (TR) 4500 min, echo time (TE) 120 min, flip angle 180°, matrix size 256^2, field of view 180 mm^2, slice thickness 4 mm, four acquisitions) were obtained through the whole length of the lesion to assess and stage the tumour radiologically. Additional sagittal and coronal T1-weighted gradient echo images (TR 65·3 min, TE 4·1 min, flip angle 75°, matrix size 256^2, field of view 300 mm^2, slice thickness 5 mm, one acquisition) were obtained as part of the survey scans.

A single-slice dynamic permeability and perfusion gradient echo data set, consisting of a proton density sequence (TR 11·7 min, TE 5 min, flip angle 5°, matrix size 256^2, field of view 300 mm^2, slice thickness 5 mm, one acquisition) and a T1- and T2*-weighted interleaved sequence (TR 11·7 min, TE$_1$ 5 min, TE$_2$ 20 min, flip angle 20°, matrix size 256^2, field of view 300 mm^2, slice thickness 5 mm, one acquisition with 42 separate studies; total scan time 7 min), was obtained through the main bulk of the tumour in the axial plane. Subsequent studies were performed in the same axial plane as the previous examination unless tumour was no longer visible, in which case the axial section was taken through what remained of the main bulk of the tumour. Data analysis was carried out off-line using software developed in-house (Magnetic Resonance Imaging Workbench)[7]. The T1 data were fitted pixel by pixel to a pharmacokinetic model described by Tofts[8] providing values of permeability surface area product. In keeping with recent recommendations[9], this measure is now termed the 'transfer constant' and indicated by the symbol K^{trans} (per minute). Regions of interest were drawn around the periphery of the tumour, after which the permeability map was calculated. Permeability values (K^{trans}) were expressed as the natural logarithmic transform because the data were non-normally distributed.

Response assessment

Radiological assessment of response, by two independent radiologists (A.R.P. and G.B.), was determined according to World Health Organization criteria. The radiologists were unaware of DCE-MRI and VEGF measurements but were aware that patients were undergoing chemoradiotherapy. The product of the length of the tumour and the maximal tumour thickness (at an anatomically consistent point in subsequent scans) was calculated for each magnetic resonance image. Complete response (CR) was defined as disappearance of tumour. Partial response (PR) was defined as a decrease of 50 per cent in the product size, and progressive disease (PD) as an increase in size of more than 25 per cent or the appearance of new lesions. Stable disease (SD) met neither the PR nor PD criteria. Patients were then classified as responders (CR and PR) and non-responders (SD or PD) by comparison of pretreatment and post-chemoradiotherapy scans.

Statistical analysis

The relationship between circulating VEGF and tumour VEGF mRNA expression was examined using a non-parametric method (Spearman correlation coefficient) as data were not normally distributed. The follow-up serum and plasma VEGF data were not normally distributed, so the Wilcoxon rank test was used to compare differences between paired samples. Tumour permeability (ln K^{trans}) and serum VEGF/platelet ratio during chemoradiotherapy data were normally distributed and so parametric tests (Pearson, paired and unpaired t tests) were used. $P < 0{\cdot}05$ was taken as significant.

Results

All tumours expressed the 121 and 165 VEGF-A isoforms. Only one tumour expressed the 189 isoform; mRNA expression of the 165 isoform and total VEGF (121 and 165 isoforms) were correlated with circulating VEGF (plasma and serum) measured by ELISA (*Table 1*). There was a significant correlation between both serum VEGF and serum VEGF/platelet ratio and tumour 165 VEGF mRNA expression ($r_S = 0{\cdot}30$ and $0{\cdot}29$, $P = 0{\cdot}02$ and $P = 0{\cdot}03$ respectively). Plasma VEGF levels showed a similar trend ($r_S = 0{\cdot}28$, $P = 0{\cdot}07$). There was no correlation between platelet count and VEGF mRNA expression.

Dynamic contrast-enhanced magnetic resonance imaging and circulating vascular endothelial growth factor levels

At presentation there was a significant correlation between DCE-MRI tumour permeability (ln K^{trans}) and serum VEGF/platelet levels ($r = 0{\cdot}48$, $P = 0{\cdot}01$) (*Fig. 1.*). Platelet count alone did not correlate with tumour permeability. This correlation between serum VEGF/platelet ratio and tumour permeability was not apparent once treatment had started. There was no correlation after chemotherapy ($r = 0{\cdot}35$, $P = 0{\cdot}19$) or chemoradiotherapy ($r = -0{\cdot}20$, $P = 0{\cdot}45$).

Sixteen patients underwent DCE-MRI during chemoradiotherapy. Typical images are shown in *Fig. 2*. Eight patients responded to chemoradiotherapy (one CR (confirmed on pathological resection) and seven PR). Eight patients did not respond (seven SD and one PD). There was a significant difference in tumour permeability at presentation between patients who responded and those who did not respond. Tumours that responded were more permeable than those that did not (mean ln K^{trans} $-0{\cdot}46$ (95 per cent confidence interval (c.i.) $-0{\cdot}29$ to $-0{\cdot}63$) and $-0{\cdot}72$ (95 per cent c.i. $-0{\cdot}54$ to $-0{\cdot}91$) respectively; $P = 0{\cdot}03$). There was no significant change in tumour permeability in either group after 12 weeks of chemotherapy. However, compared with pretreatment values there was a significant decrease in permeability in responsive tumours at the end of chemoradiotherapy (mean ln K^{trans} $-0{\cdot}46$ (95 per cent c.i. $-0{\cdot}29$ to $-0{\cdot}63$) and $-0{\cdot}86$ (95 per cent c.i. $-0{\cdot}62$ to $-1{\cdot}10$) respectively; $P = 0{\cdot}04$) (*Fig. 3*).

Table 1 Spearman correlation of tumour vascular endothelial (VEGF) growth factor messenger RNA expression in 57 colorectal cancers with circulating VEGF levels

		r_S	
	n	165 isoform	Total VEGF
Plasma VEGF (pg/ml)	41*	0·28	0·25
Serum VEGF (pg/ml)	57	0·30†	0·30†
Platelet count (10^9/l)	57	0·14	0·15
Serum VEGF/platelet (pg/10^6)	57	0·29†	0·27†

*Sixteen tumours were excluded because plasma levels were less than 9 pg/ml (lower limit of enzyme-linked immunosorbent assay sensitivity). †Significant correlation ($P \leqslant 0{\cdot}05$)

Changes in vascular endothelial growth factor during chemoradiotherapy

Eighteen patients underwent chemoradiotherapy and had serial VEGF measurements performed during treatment. CT was used to assess the response in the two patients who were unable to undergo MRI. Nine patients responded to treatment (CR and PR) and nine patients did not (SD and PD).

There was a wide range of serum VEGF/platelet levels seen in the 18 patients before treatment (0·25–5·53 pg/10^6); however, each patient's value at presentation served as his or her own internal control for subsequent serial measurements. The measurements of serum VEGF/platelet ratio

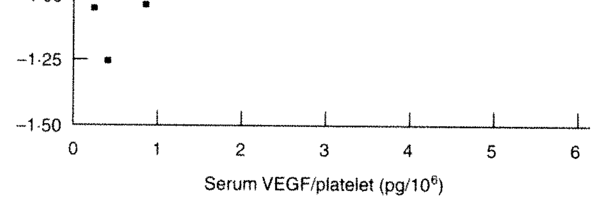
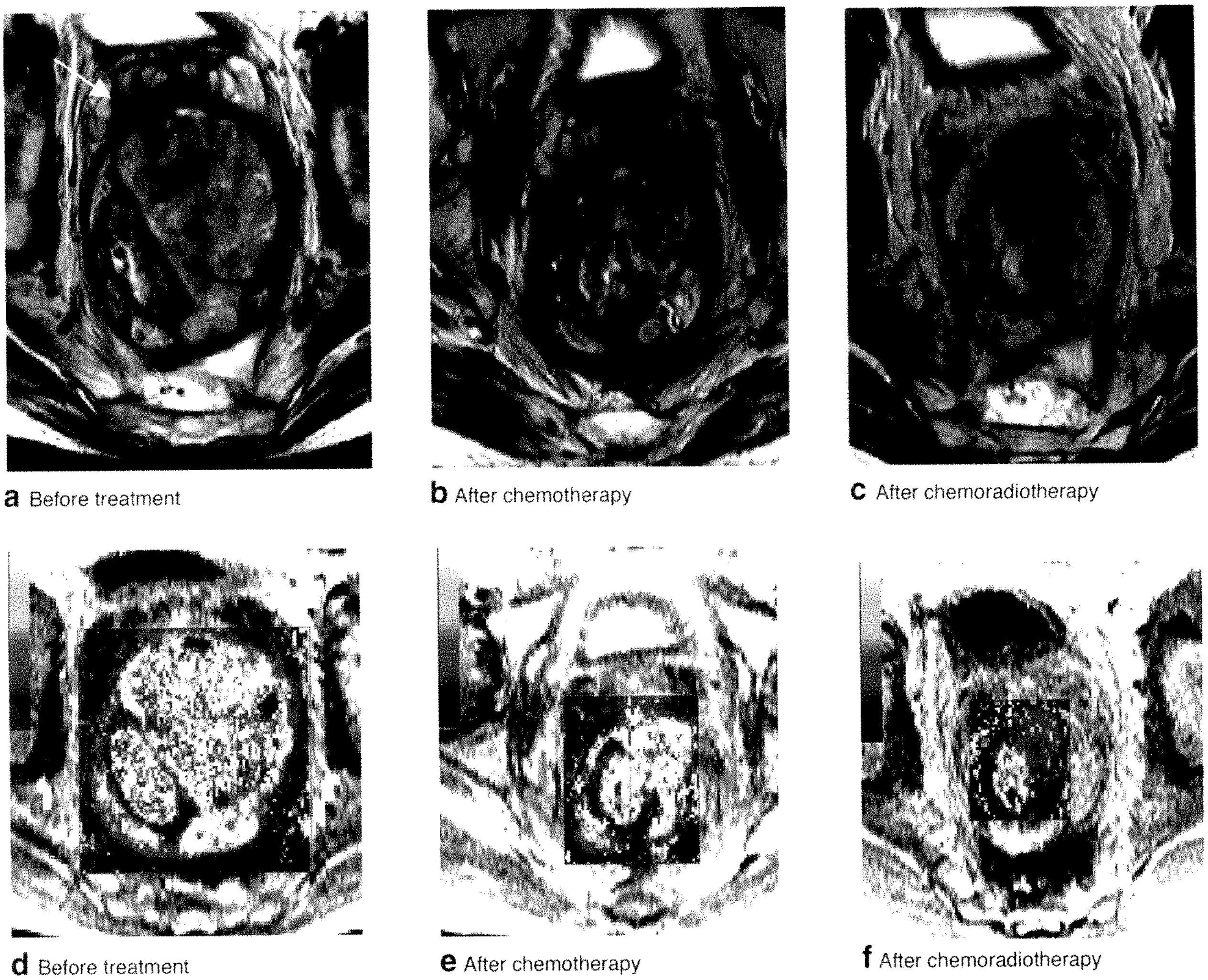


Fig. 1 Pearson correlation of pretreatment serum vascular endothelial growth factor (VEGF)/platelet ratio and tumour permeability (ln K^{trans}) in 28 patients with T_3/T_4 rectal cancer


a Before treatment

b After chemotherapy

c After chemoradiotherapy

d Before treatment

e After chemotherapy

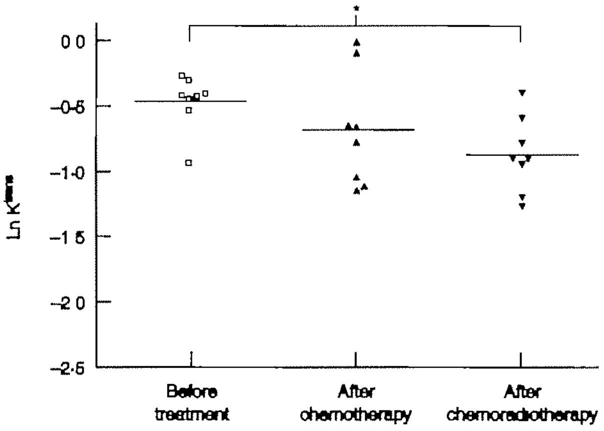
f After chemoradiotherapy

Fig. 2 T2-weighted anatomical images of a T_4 tumour with seminal vesicle involvement (indicated by arrow) **a** at presentation, **b** after 12 weeks of chemotherapy and **c** 4 weeks after chemoradiotherapy. **d–f** Corresponding T1-weighted permeability maps; **d** shows heterogeneous high permeability in the tumour (ln K^{trans} −0·44) with a large number of pixels that fail to show colour (areas of modelling failure due to high vascular volume). **e** After chemotherapy, high permeability continues to be seen but with less pixel failure (ln K^{trans} −1·11), whereas in **f**, after chemoradiotherapy, only the centre of the tumour shows high permeability (ln K^{trans} −1·25)

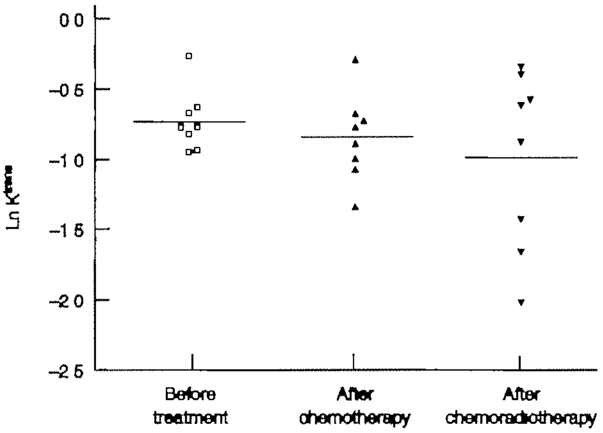
during the various phases of chemotherapy and chemoradiotherapy were averaged to obtain a single mean value, which was then compared with the value at presentation to calculate the change during each phase of treatment. A final blood sample was taken 4–6 weeks after termination of chemoradiotherapy at the time of the final magnetic resonance scan.

Pretreatment there was no difference in serum VEGF/platelet ratio between responsive and non-responsive patients (1·92 and 1·28 pg/10^6 respectively, $P = 0·32$). There was a fall in serum VEGF/platelet ratio in responsive patients after both chemotherapy and chemoradiotherapy but this did not reach statistical significance. In contrast, patients who did not respond showed a rise in serum VEGF/platelet ratio after chemotherapy and chemoradiotherapy ($P = 0·19$ and $P = 0·06$ respectively) (*Fig. 4*). Four weeks after chemoradiotherapy, mean serum VEGF/platelet levels were significantly higher in patients who did not respond compared with pretreatment levels (1·02 and 0·00 pg/10^6 respectively; $P < 0·01$). At the same timepoint, serum VEGF/platelet levels were lower than initial values in patients who responded, but these differences were not significant.

Comparison of groups of patients who responded and those who did not showed that during the chemotherapy phase of treatment there was no significant difference in the



a Responsive tumours



b Unresponsive tumours

Fig. 3 Tumour permeability (ln K^{trans}) of **a** responsive tumours and **b** unresponsive tumours measured by dynamic contrast-enhanced magnetic resonance imaging after chemotherapy and chemoradiotherapy. Horizontal bars represent mean values. $^{*}P = 0{\cdot}04$ (paired *t* test)

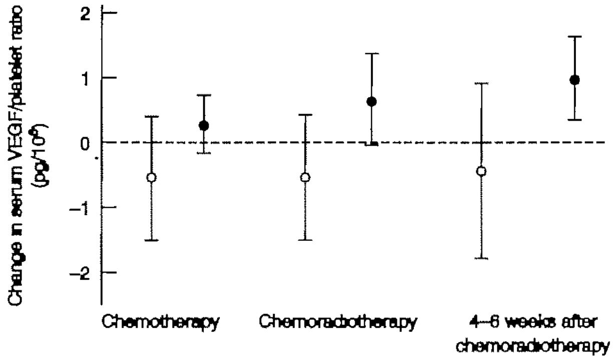


Fig. 4 Change in serum vascular endothelial growth factor (VEGF)/platelet ratio from pretreatment levels in patients with responsive (○; $n = 9$) or unresponsive (●; $n = 9$) tumours during chemotherapy and chemoradiotherapy, and 4–6 weeks after treatment. Values are mean (95 per cent confidence intervals)

change in serum VEGF/platelet levels (− 0·56 and 0·28 pg/10^6 respectively; $P = 0{\cdot}09$). However, there was a significant difference between those who responded and those who who did not during chemoradiotherapy (− 0·55 and 0·69 pg/10^6 respectively; $P = 0{\cdot}03$). This difference was sustained 4–6 weeks later (− 0·41 and 1·02 pg/10^6 respectively; $P < 0{\cdot}05$) (*Fig. 4*).

Follow-up serum and plasma vascular endothelial growth factor measurements

There was a significant fall in plasma VEGF levels in 52 patients who were disease free at 12 months compared with preoperative levels (median 9·0 (interquartile range (i.q.r.) 9·0–16·7) and 13·7 (i.q.r. 9·0–28·4) pg/ml respectively; $P < 0{\cdot}01$). There was a significant increase in plasma VEGF concentration in 18 patients with progressive or recurrent disease compared with pretreatment values (median 52·5 (i.q.r. 24·1–101·6) and 26·3 (i.q.r. 9·0–51·8) pg/ml respectively; $P = 0{\cdot}02$).

Serum VEGF levels decreased significantly in 35 patients who were disease free at 12 months compared with preoperative levels (median 211·5 (i.q.r. 111·3–335·3) and 275·7 (i.q.r. 192·9–459·7) pg/ml respectively; $P < 0{\cdot}01$). This change reflected a significant fall in platelet count after curative surgical resection (214 (i.q.r. 189–278) and 284 (i.q.r. 215–372) 10^9/l; $P < 0{\cdot}01$). There was no significant change in serum VEGF level or platelet count in patients with progressive or recurrent disease.

After correcting for variation in platelet count by calculating the serum VEGF/platelet ratio, there was a significant rise in serum VEGF/platelet count in 16 patients with progressive or recurrent disease (median 1·82 (i.q.r. 1·00–3·06) and 1·20 (i.q.r. 0·84–2·02) pg/10^6/ml respectively; $P = 0{\cdot}02$). There was a fall in serum VEGF/platelet ratio after curative resection at 12 months but this did not reach statistical significance.

Discussion

The importance of angiogenesis in tumour growth has been established. However, the methods used to assess angiogenesis in clinical practice have relied mainly on immunostaining of postoperative specimens to count either microvessel density or to assess VEGF expression. Despite an international consensus on methodology for assessing microvessel density[10], there still remain variations in antibody usage and counting techniques. This has produced conflicting results and it is unclear, in colorectal cancer, whether high microvessel density is of good prognostic significance[11] or not[12–14].

Indirect methods of assessing angiogenesis, such as measurement of blood levels of cytokines and DCE-MRI, are now being used increasingly. However, previous studies, with small patient numbers, have failed to establish a relationship between blood and tumour VEGF levels[3,15]. Blood levels of VEGF do appear to correlate with increasing microvessel density in breast cancer[16] and colorectal liver metastasis[17]. In the present study, which employed quantitative (ELISA) and semiquantitative (RT-PCR) methods, there was a significant correlation between tumour VEGF mRNA and serum VEGF, suggesting that serum VEGF levels do reflect tumour VEGF levels and may therefore serve as a surrogate marker of tumour angiogenesis.

In colorectal cancer, serum VEGF has been found to correlate with disease stage[4] and levels at presentation may be useful in determining those patients at risk of metastatic spread and who may therefore benefit from adjuvant treatment[18]. In this study there were significant changes in plasma VEGF with recurrent/progressive disease and curative resection, but the number of measurements that are at the lower end of the ELISA sensitivity remains a problem[4]. Serum VEGF/platelet values increased significantly with recurrent/progressive disease and fell with curative resection. That the latter observation did not reach statistical significance may be due to insufficient numbers.

This is the first study to assess serial circulating VEGF changes during chemoradiotherapy. Pretreatment serum VEGF/platelet values were not significantly different between patients who responded and those who did not, and cannot be used to predict response. These findings are similar to results in patients with ovarian carcinoma[19], but contrast with results found in patients with small cell lung cancer[20] and lymphoma[21]. Four weeks after finishing treatment, serum VEGF/platelet levels were significantly raised in non-responders compared with pretreatment values. VEGF is released from irradiated cells and is thought to have a protective effect against radiation-induced damage[22]. Interestingly, the present study demonstrated that the non-responsive patient group had a significant increase in serum VEGF/platelet ratio compared with the responsive group during the chemoradiotherapy phase of treatment, which may represent a resistance mechanism, protecting tumours from the effects of radiotherapy.

In this study there was a significant correlation between circulating VEGF levels and DCE-MRI permeability at presentation, which adds support to studies by Knopp *et al.*[23], who who found that VEGF staining in breast tumours correlated with MRI global permeability. Thus VEGF may be important in DCE-MRI permeability studies, although this has not been demonstrated in cervical cancer[24].

Previous studies that compared microvessel density and immunostaining with response to chemotherapy and chemoradiotherapy have reported varying results[25–28]. The disadvantage of microvessel density and immunohistochemical studies compared with DCE-MRI is that the former produce anatomical data only and are prone to biopsy sampling errors. DCE-MRI measurements reflect both microvessel density and permeability variables, and therefore provide functional and, theoretically, more realistic *in vivo* data.

The use of DCE-MRI in assessing tumour angiogenesis has been shown to be predictive of tumour response[29] and of value in assessing prognosis[30]. Recently, DCE-MRI studies in 11 patients with T_3 rectal cancer receiving preoperative radiotherapy showed that high-permeability tumours were associated with nodal downstaging, with a trend towards downstaging of the primary tumour[31]. The present study has shown that responsive rectal tumours have a significantly greater permeability than non-responsive tumours. This suggests that a permeable vasculature may provide better access for chemotherapy drugs, and have better oxygenation[32] and hence higher radiosensitivity[33]. Future studies that measure changes in tumour drug levels, with variable tumour endothelial cell permeability and radiotherapy, may confirm this.

Following chemoradiotherapy, but not chemotherapy, there was a significant decrease in DCE-MRI permeability in responsive tumours. This may reflect a decrease in microvessel density[34,35]. Irradiation causes a decrease in microvessel density with no effect on VEGF expression in a rat glioma model, suggesting that the antivascular effect may be mediated by direct antiproliferative effects on endothelial cells[36]. However, tumour vasculature contains many immature vessels (those without pericytes or smooth muscle), by definition the most permeable, that are sensitive to VEGF withdrawal[37]. The decrease in K^{trans} in responsive tumours may reflect loss of these immature vessels, whereas non-responsive tumours, which had a significant rise in circulating VEGF levels, showed no change in K^{trans}. It may be assumed that increased circulating VEGF concentration supported the survival of these immature vessels.

The initial relationship between circulating VEGF levels and MRI permeability was lost during chemotherapy and chemoradiotherapy. This may be explained by a decrease in microvessel density with unchanging tumour VEGF expression[36] or by differences in the parameters that these two indirect methods actually measure. MRI has the benefit of determining purely localized tumour-associated angiogenesis, whereas serum VEGF levels may include non-tumour-derived cytokine. Previous studies that have measured changes in serum VEGF levels following colorectal resection have shown that loss of tumour-derived VEGF is counterbalanced by rises in VEGF concentration in response to surgical trauma. Therefore serum VEGF levels reflect total VEGF from both tumour- and host-derived sources[4]. Chemotherapy and chemoradiotherapy may alter the ratio of tumour- and host-derived VEGF due to normal tissue damage and repair processes, and subsequently total levels present in the circulation.

In summary, the two indirect methods of assessing angiogenesis studied here (circulating VEGF concentration and dynamic MRI) measure different and contrasting aspects of angiogenic response during chemoradiotherapy. Serum VEGF measurements encompass changes in both tumour-derived VEGF and host cell-derived VEGF. The finding that highly permeable tumours respond better to chemoradiotherapy than tumours with low permeability is potentially of great clinical importance. Patients with high-permeability tumours could be offered chemoradiotherapy before operation, whereas those with low-permeability tumours could be offered alternative treatments[38].

Acknowledgements

The authors acknowledge the help of Dr Andrew Norman with the statistical analysis, and Dr Mark Hill, Dr David Cunningham and Professor Janet Husband for their contribution to the study. This work was funded by a *BJS* Research Bursary.

References

1 Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990; **82:** 4–6.

2 Brasch RC, Li KC, Husband JE, Keogan MT, Neeman M, Padhani AR *et al.* *In vivo* monitoring of tumor angiogenesis with MR imaging. *Acad Radiol* 2000; 7: 812–23.

3 Balsari A, Maier JA, Colnaghi MI, Menard S. Correlation between tumor vascularity, vascular endothelial growth factor production by tumor cells, serum vascular endothelial growth factor levels, and serum angiogenic activity in patients with breast carcinoma. *Lab Invest* 1999; **79:** 897–902.

4 George ML, Eccles SA, Tutton MG, Abulafi AM, Swift RI Correlation of plasma and serum vascular endothelial growth factor levels with platelet count in colorectal cancer: clinical evidence of platelet scavenging? *Clin Cancer Res* 2000; **6:** 3147–52.

5 Ross P, Norman A, Cunningham D, Webb A, Iveson T, Padhani A *et al.* A prospective randomised trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. *Ann Oncol* 1997; **8:** 995–1001.

6 George ML, Tutton MG, Janssen F, Arnaout A, Abulafi AM, Eccles SA *et al.* VEGF-A, C and D in colorectal cancer progression. *Neoplasia* 2001; **3:** 420–7.

7 Parker GJ, Suckling J, Tanner SF, Padhani AR, Revell PB, Husband JE *et al.* Probing tumor microvascularity by measurement, analysis and display of contrast agent uptake kinetics. *J Magn Reson Imaging* 1997; **7:** 564–74.

8 Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging* 1997; **7:** 91–101.

9 Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV *et al.* Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999, **10:** 223–32.

10 Vermeulen PB, Gasparini G, Fox SB, Toi M, Martin L, McCulloch P *et al.* Quantification of angiogenesis in solid human tumours. an international consensus on the methodology and criteria of evaluation. *Eur J Cancer* 1996; **32A:** 2474–84.

11 Abdalla SA, Behzad F, Bsharah S, Kumar S, Amini SK, O'Dwyer ST *et al.* Prognostic relevance of microvessel density in colorectal tumours. *Oncol Rep* 1999; **6:** 839–42.

12 Choi HJ, Hyun MS, Jung GJ, Kim SS, Hong SH. Tumor angiogenesis as a prognostic predictor in colorectal carcinoma with special reference to mode of metastasis and recurrence. *Oncology* 1998; **55:** 575–81.

13 Takebayashi Y, Aklyama S, Yamada K, Akiba S, Aikou T. Angiogenesis as an unfavorable prognostic factor in human colorectal carcinoma. *Cancer* 1996; **78:** 226–31.

14 Vermeulen PB, Van den Eynden GG, Huget P, Goovaerts G, Weyler J, Lardon F *et al.* Prospective study of intratumoral microvessel density, p53 expression and survival in colorectal cancer. *Br J Cancer* 1999; **79:** 316–22.

15 Takano S, Yoshii Y, Kondo S, Suzuki H, Maruno T, Shirai S *et al.* Concentration of vascular endothelial growth factor in the serum and tumor tissue of brain tumor patients. *Cancer Res* 1996; **56:** 2185–90.

16 Yamamoto Y, Toi M, Kondo S, Matsumoto T, Suzuki H, Kitamura M *et al* Concentrations of vascular endothelial growth factor in the sera of normal controls and cancer patients. *Clin Cancer Res* 1996; **2:** 821–6.

17 Davies MM, Jonas SK, Kaur S, Allen-Mersh TG. Plasma vascular endothelial but not fibroblast growth factor levels correlate with colorectal liver mestastasis vascularity and volume. *Br J Cancer* 2000; **82:** 1004–8.

18 Chin KF, Greenman J, Gardiner E, Kumar H, Topping K, Monson J. Pre-operative serum vascular endothelial growth factor can select patients for adjuvant treatment after curative resection in colorectal cancer. *Br J Cancer* 2000; **83:** 1425–31.

19 Abendstein B, Daxenbichler G, Windbichler G, Zeimet AG, Geurts A, Sweep F *et al.* Predictive value of uPA, PAI-1, HER-2 and VEGF in the serum of ovarian cancer patients. *Anticancer Res* 2000; **20:** 569–72.

20 Salven P, Ruotsalainen T, Mattson K, Joensuu H. High pre-treatment serum level of vascular endothelial growth factor (VEGF) is associated with poor outcome in small-cell lung cancer. *Int J Cancer* 1998; **79:** 144–6.

21 Salven P, Teerenhovi L, Joensuu H. A high pretreatment serum vascular endothelial growth factor concentration is associated with poor outcome in non-Hodgkin's lymphoma. *Blood* 1997; **90:** 3167–72.

22 Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM *et al.* Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res* 1999; **59:** 3374–8.

23 Knopp MV, Weiss E, Sinn HP, Mattern J, Junkermann H, Radeleff J *et al.* Pathophysiologic basis of contrast enhancement in breast tumors. *J Magn Reson Imaging* 1999; **10:** 260–6.

24 Hawighorst H, Libicher M, Knopp MV, Moehler T, Kauffmann GW, Kaick G. Evaluation of angiogenesis and perfusion of bone marrow lesions: role of semiquantitative and quantitative dynamic MRI. *J Magn Reson Imaging* 1999; **10:** 286–94.

25 Gasparini G, Bevilacqua P, Bonoldi E, Testolin A, Galassi A, Verderio P *et al.* Predictive and prognostic markers in a series of patients with head and neck squamous cell invasive carcinoma treated with concurrent chemoradiation therapy. *Clin Cancer Res* 1995; **1:** 1375–83.

26 Giatromanolaki A, Koukourakis MI, Georgoulias V, Gatter KC, Harris AL, Fountzilas G. Angiogenesis *vs.* response after combined chemoradiotherapy of squamous cell head and neck cancer. *Int J Cancer* 1999; **80:** 810–17.

27 Boku N, Chin K, Hosokawa K, Ohtsu A, Tajiri H, Yoshida S *et al.* Biological markers as a predictor for response and prognosis of unresectable gastric cancer patients treated with 5-fluorouracil and *cis*-platinum. *Clin Cancer Res* 1998; **4:** 1469–74.

28 Takiuchi H, Hirata I, Kawabe S, Egashira Y, Katsu K. Immunohistochemical expression of vascular endothelial growth factor can predict response to 5-fluorouracil and cisplatin in patients with gastric adenocarcinoma. *Oncol Rep* 2000; **7:** 841–6.

29 Knopp MV, Brix G, Junkermann HJ, Sinn HP. MR mammography with pharmacokinetic mapping for monitoring of breast cancer treatment during neoadjuvant therapy. *Magn Reson Imaging Clin North Am* 1994; **2:** 633–58.

30 Hawighorst H, Weikel W, Knapstein PG, Knopp MV, Zuna I, Schonberg SO *et al.* Angiogenic activity of cervical carcinoma: assessment by functional magnetic resonance imaging-based parameters and a histomorphological approach in correlation with disease outcome. *Clin Cancer Res* 1998; **4:** 2305–12.

31 de Vries A, Griebel J, Kremser C, Judmaier W, Gneiting T, Debbage P *et al.* Monitoring of tumor microcirculation during fractionated radiation therapy in patients with rectal carcinoma: preliminary results and implications for therapy. *Radiology* 2000; **217:** 385–91.

32 Cooper RA, Carrington BM, Loncaster JA, Todd SM, Davidson SE, Logue JP *et al.* Tumour oxygenation levels correlate with dynamic contrast-enhanced magnetic resonance imaging parameters in carcinoma of the cervix. *Radiother Oncol* 2000; **57:** 53–9.

33 Protopapa E, Delides GS, Revesz L. Vascular density and the response of breast carcinomas to mastectomy and adjuvant chemotherapy. *Eur J Cancer* 1993; **29A:** 1391–3.

34 Torres C, Wang H, Turner J, Shahsafaei A, Odze RD. Prognostic significance and effect of chemoradiotherapy on microvessel density (angiogenesis) in esophageal Barrett's esophagus-associated adenocarcinoma and squamous cell carcinoma. *Hum Pathol* 1999; **30:** 753–8.

35 Ueda M, Ueki K, Kumagai K, Terai Y, Okamoto Y, Ueki M *et al.* Apoptosis and tumor angiogenesis in cervical cancer after preoperative chemotherapy. *Cancer Res* 1998; **58:** 2343–6.

36 Johansson M, Bergenheim AT, Widmark A, Henriksson R. Effects of radiotherapy and estramustine on the microvasculature in malignant glioma. *Br J Cancer* 1999; **80:** 142–8.

37 Benjamin LE, Golijanin D, Itin A, Pode D, Keshet E. Selective ablation of immature blood vessels in established human tumors follows vascular endothelial growth factor withdrawal. *J Clin Invest* 1999; **103:** 159–65.

38 Mauceri HJ, Hanna NN, Beckett MA, Gorski DH, Staba MJ, Stellato KA *et al.* Combined effects of angiostatin and ionizing radiation in antitumour therapy. *Nature* 1998; **394:** 287–91.

Short note

Ileal neoappendicostomy for antegrade colonic irrigation

P. Christensen, S. Buntzen, K. Krogh and S. Laurberg

Surgical Research Unit, Department of Surgery L, Section AAS, University Hospital of Aarhus, Aarhus, Denmark
Correspondence to: Dr P. Christensen, Surgical Research Unit, Department of Surgery L, Aarhus Amtssygehus, Tage Hansens Gade 2, DK-8000 Aarhus C, Denmark (e-mail: Piz@dadlnet.dk)

Paper accepted 31 August 2001

Introduction

The use of an appendicostomy for administration of antegrade enemas has proven to be safe and effective in selected patients with faecal incontinence and constipation[1–3]. When the appendix is not available a number of other techniques have been used to create a substitute for the appendix[1,2,4,5]. However, the morbidity with these procedures is considerable, including leakage of mucus or faeces and stomal stenosis. The aim of this study was to evaluate preliminary results with a new ileal neoappendicostomy.

Patients and methods

Surgical technique

The terminal ileum is divided with an 80-mm GIA stapling device (USSC, North Haven, Connecticut, USA). A 12-Fr balloon catheter is introduced through the ileocaecal valve into the caecum via a small incision at the mesenteric border of the divided distal terminal ileum. The balloon is inflated to help identify the ileocaecal valve. The calibre of the distal terminal ileum is reduced by resection along the antimesenteric border, preserving the ileocaecal valve (*Fig. 1*). An ileocolonic anastomosis is made from the proximal terminal ileum and the ascending colon. The ileal conduit is exteriorized using a V–Y plasty in the skin[2]. Finally, the caecum is sutured to the back of the anterior abdominal wall. Following the procedure, a 10-Fr silicone catheter is left *in situ* for 2 weeks.

Patients

From September 1999 to November 2000 nine patients with severe colorectal dysfunction underwent the operation as described (all women; median age 50 (range 29–69) years). All patients were followed prospectively. In three patients a sigmoid colostomy was added to the procedure. Five patients had been incontinent to solid stools daily or several times per week. In two of these patients, faecal incontinence was the result of spinal cord injury, in two patients there was anal sphincter insufficiency and in one patient incontinence followed surgery for rectal prolapse. Four patients suffered from severe constipation.

Results

After a median follow-up of 10 (range 3–20) months, eight of nine patients still used the ileal neoappendicostomy. In two patients the neoappendicostomy was completely continent. Six patients had minor liquid reflux, two patients had small leakage of gas, and two patients complained of a periodic bad smell from the ileal conduit. All patients covered the stoma with a simple wound bandage. The stoma was easy to catheterize in six patients, narrow in one patient, and one patient had a stenosis of the ileal conduit requiring dilatation under general anaesthesia. To prevent further trouble a gastrotomy tube (MIC-KEY; Ballard Medical Products, Draper, Utah, USA) was inserted.

With regular antegrade colonic irrigation faecal incontinence was either absent or very much reduced, and constipation was treated successfully in three of four patients. One patient had an unsatisfactory result from the irrigation procedure. Four patients reported transient side-effects during washout such as chills, mild abdominal

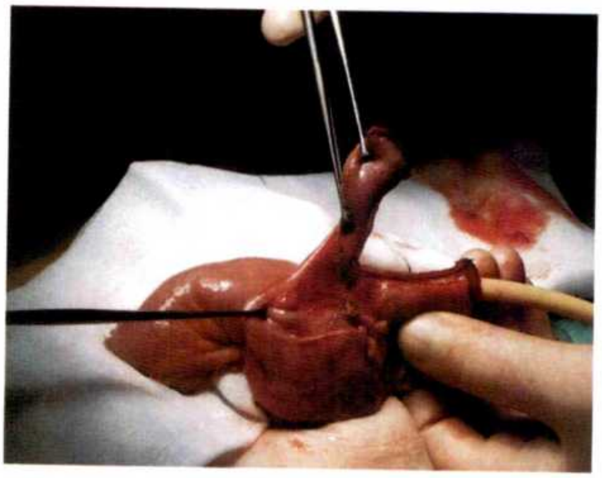


Fig. 1 The terminal ileum is divided approximately 6 cm from the ileocaecal valve. The proximal part of the terminal ileum is situated to the left. A 12-Fr catheter is introduced via the distal part of the terminal ileum through the ileocaecal valve into the caecum. The balloon is inflated to help identify the ileocaecal valve. The calibre of the distal terminal ileum is reduced by resection along the antimesenteric border. At the ileocaecal junction the antimesenteric part of the terminal ileum is resected, preserving the ileocaecal valve

cramps and nausea. Four patients had no side-effects. Overall satisfaction was very high in three patients, high in four and very poor in one patient. In total, seven of nine patients had significant improvement in bowel function.

Discussion

The appendicostomy remains the first-choice procedure for administration of antegrade enemas. If the appendix is no longer available it is possible to create an ileal conduit with the distal terminal ileum[5] with the ileocaecal valve acting as a passive antireflux mechanism.

The present study presents a new technique that involves reduction of the calibre of the ileal conduit and use of a V–Y flap to create the stoma. These elements further add to the antireflux mechanism of the ileocaecal valve. By reducing the calibre of the distal terminal ileum from a diameter of approximately 30 mm to 3 mm the surface area of the mucosa is also reduced by a factor of 10, thereby reducing problems with secretions.

Although six of eight patients reported leakage through the ileal conduit it was minor in all cases and easily controlled with a simple wound bandage. None of the patients felt that it was a problem. A common difficulty with both the appendicostomy and other types of neoappendicostomy is stenosis[1,2]. In the present study one patient had a stenosis that required dilatation.

The present study confirms that treatment with antegrade colonic enemas in adults is well tolerated with only transient side-effects[2,3]. However, a median follow-up of 10 months is still short and long-term follow-up is needed to ensure that initial promising results are maintained. If the appendix is no longer available the new ileal neoappendicostomy is technically simple and provides good functional results for administration of antegrade enemas.

References

1 Malone PS, Curry JI, Osborne A. The antegrade continence enema procedure why, when and how? *World J Urol* 1998; **16:** 274–8.
2 Krogh K, Laurberg S. Malone antegrade continence enema for faecal incontinence and constipation in adults. *Br J Surg* 1998; **85:** 974–7.
3 Christensen P, Kvitzau B, Krogh K, Buntzen S, Laurberg S. Neurogenic colorectal dysfunction – use of new antegrade and retrograde colonic wash-out methods. *Spinal Cord* 2000; **38:** 255–61.
4 Monti PR, Lara RC, Dutra MA, de Carvalho JR. New techniques for construction of efferent conduits based on the Mitrofanoff principle. *Urology* 1997; **49:** 112–15.
5 Marsh PJ, Kiff ES. Ileocaecostomy: an alternative surgical procedure for antegrade colonic enema. *Br J Surg* 1996; **83:** 507–8.

Original article

Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection

R. M. H. Roumen, G. P. Kuijt, I. H. Liem* and M. W. P. M. van Beek†

Departments of Surgery, *Nuclear Medicine and †Pathology, Saint Joseph Hospital, PO Box 7777, 5500 MB Veldhoven, The Netherlands
Correspondence to: Dr R. M. H. Roumen (e-mail: rroumen@sjz.nl)

Background: The sentinel node biopsy technique for breast cancer has been validated extensively in phase I and II studies. However, no data from phase III randomized clinical studies are available. It remains controversial whether a histologically negative sentinel node biopsy without further axillary dissection can be considered to be good clinical practice.

Methods: One hundred consecutive patients with breast cancer who had a negative sentinel node biopsy without additional axillary dissection were studied prospectively between 1997 and 2000 in order to identify tumour recurrence and to assess the morbidity of the sentinel node procedure. Special attention was paid to axillary or locoregional recurrence, distant metastases and overall survival. One year after the procedure patients were sent a questionnaire to assess any functional impairment of the arm or shoulder.

Results: Median follow-up was 24 (range 16–40) months. One patient had an axillary relapse 14 months after the initial diagnosis of breast cancer. She died after 2 years from metastatic disease. There were no other local axillary recurrences. There was a 94 per cent response rate to the questionnaire. Twelve patients developed mild disabilities, of whom two said that they had to change their hobbies, sports or daily activities owing to the sentinel node procedure. No patient developed lymphoedema or needed physiotherapy after the operation.

Conclusion: When strict criteria for the sentinel node biopsy procedure are used, the sentinel node biopsy without further axillary dissection after a negative histological investigation is a safe procedure. It may therefore be considered to be the standard of care for the treatment of patients with breast cancer.

Paper accepted 13 August 2001

British Journal of Surgery 2001, **88**, 1639–1643

Introduction

In patients with operable primary breast cancer, complete axillary dissection is still considered to be the standard of surgical care. However, the minimally invasive sentinel node biopsy provides an attractive alternative to this procedure, because it reduces morbidity substantially. The main reason for performing a complete axillary dissection in breast cancer is for diagnostic purposes. When the axillary lymph nodes are positive for metastatic disease, adjuvant treatment is necessary, while the complete removal of nodal metastases might be therapeutic and contribute to the surgical cure of the patient. Where axillary nodes are negative, the additional value of a complete dissection of all nodal levels is questioned. Such patients are very unlikely to benefit from complete removal of the axillary lymph nodes.

Until now the sentinel node biopsy *only* (no additional axillary dissection if the sentinel node is negative for metastatic disease) has been a matter of debate and some authors are opposed to this procedure as the standard of care[1,2]. Their main concern relates to false-negative sentinel node biopsies and their consequences.

The present study provides data about the quality control and regular follow-up of 100 consecutive patients who underwent a sentinel node biopsy as a sole procedure and who did not have an additional complete axillary dissection.

Patients and methods

From the end of 1997 until June 2000, one hundred consecutive patients with operable primary breast cancer, who underwent a sentinel node biopsy that revealed a negative histological status, were studied prospectively.

Sentinel node biopsy was performed according to a protocol that included only patients with single tumours less than 3 cm in diameter, without clinically suspicious palpable axillary nodes and without clinical signs of distant metastases. Patients were informed about the risk and the technique, after which informed consent was obtained. During the interval in question, 143 patients underwent a sentinel node biopsy of which 43 (30 per cent) were found to be positive.

The biopsy technique has been described previously and includes the use of peritumourally injected technetium-labelled human albumin (Solco R/Nanocoll; Sorin Biomedica Diagnostics, Vercelli, Italy) with lymphoscintigraphy, together with periareolar injection of vital blue dye (Patent Blue V, 2·5 per cent solution; Laboratoire Guerbet, Aulnay-sous-Bois, France)[3,4]. The sensitivity of this procedure was 95 per cent[3]. Harvested sentinel nodes were sectioned serially: small nodes (less than 4 mm) at three levels and larger nodes at six levels. The slides were then stained with haematoxylin and eosin and immunostained with Pan Ab-3 anticytokeratin (Neomarkers, Fremont, California, USA). In the case of a positive sentinel node, patients were offered a complete axillary lymph node dissection. All patients were seen at follow-up after 3 months and subsequently every 6 months. Special attention was paid to possible axillary recurrent disease, locoregional recurrences, distant metastases and new breast cancers.

All patients without recurrent disease or distant metastases were asked to complete a questionnaire assessing postoperative functional disability of the arm and shoulder (*Table 1*). The questionnaires were sent to all patients at least 12 months after the primary surgical procedure.

Table 1 Questionnaire responses

		No. of affirmative responses
1	Do you have any discomfort as a result of the axillary scar?	5 (6)
2	Has the function of your shoulder and/or arm changed since the axillary operation?	10 (11)
3	Did you develop a disability in your arm after the axillary operation?	9 (10)
4	Do you have any (new) pain in the axilla or shoulder since the operation?	12 (13)
5	Did you develop any form of lymphoedema?	0 (0)
6	Has there been a change or loss of sensation in the axilla?	12 (13)
7	Did you have to change your hobbies or sports:	
	Due to the operation in the axilla?	2 (2)
	Due to the breast operation?	10 (11)
8	Was there a need for physical therapy as a result of the axillary operation?	0 (0)

Values in parentheses are percentages. The questionnaire was sent to all patients without (axillary) recurrence or distant metastases (*n* = 96; response rate 94 per cent (90 of 96))

Results

Table 2 shows the initial patient and tumour characteristics of the negative sentinel node biopsy population without further axillary dissection between 1997 and 2000. Median follow-up was 24 (range 16–40) months. During this period, 99 of the 100 patients did not develop a local axillary relapse.

However, one 46-year-old patient was found to have residual axillary disease at 14 months after the initial sentinel node procedure. An excisional biopsy was performed in June 1998, and an invasive ductal carcinoma grade II with a diameter of 8 mm was diagnosed. The

Table 2 Demographic data of 100 patients with a negative sentinel node biopsy

Age (years)*	59 (33–86)
Menopausal status	
Premenopausal	33
Postmenopausal	66
Male gender	1
Type of surgery	
Ablation	20
Breast conserving†	80
Tumour size (mm)*	15 (3–31)
Histological grade	
I	42
II	23
III	35
Histology of tumour	
Ductal	74
Lobular	16
Mixed or other	10
Receptor status	
Oestrogen receptor positive	73
Progesterone receptor positive	65
Unknown	9
Adjuvant therapy	
Chemotherapy	13
Hormonal therapy	39
Recurrent disease	
Axilla	1
Breast/scar	1
Metastatic disease	
Bone	1
Lung	1
Lung, bone and brain	1
Deaths	
Stroke	1
Metastatic disease	2

*Values are median (range). †All patients received radiotherapy of the breast; no radiotherapy of the axilla was given. Mean and median number of sentinel node biopsies per patient was 2 (range 1–4) patient then had a sentinel node biopsy (one sentinel node) together with a re-excision of the primary tumour because of a residual ductal carcinoma *in situ*. In September 1998 an additional mastectomy with primary reconstruction using the expander technique was performed. One year later the patient presented with axillary pain and a palpable lesion. A complete axillary dissection showed more than ten positive lymph nodes. Locoregional radiotherapy and hormonal treatment (ovariectomy as well as tamoxifen) was started, but within 2 months the patient developed recurrent disease with pulmonary and bone metastases. In August 2000, 26 months after the initial diagnosis, she died from brain metastases.

Another patient, aged 44 years, developed a local recurrence in the skin 9 months after the initial operation, which was a two-stage mastectomy for widespread invasive lobular carcinoma. At that time, no axillary recurrence was found. She was treated with tamoxifen, leading to a partial remission. Four months later a right colectomy was performed because of an invasive colon carcinoma (pT$_2$ N$_0$ M$_x$). Two months after the colectomy, there was an increase in the local mammary skin recurrence and a clinically suspected and pathologically confirmed axillary lymph node had developed. Locoregional radiotherapy was instigated.

In all, three patients have died: the abovementioned 46-year-old patient from metastatic disease, another 80-year-old patient with bone metastases but without signs of locoregional recurrence, and one 63-year-old patient from a stroke.

Of the 96 patients surviving without residual or recurrent axillary disease, 90 returned the questionnaire (94 per cent response rate). *Table 1* shows the responses. Only a minority of the patients complained of mild functional loss or pain in the shoulder or arm. Remarkably none of the patients developed any form of arm oedema or needed additional physiotherapy because of shoulder complaints. Twelve patients experienced some loss of sensation in the axilla, most probably owing to a lesion of the intercostobrachial nerve.

Discussion

The main purpose of a sentinel node biopsy is to avoid an unnecessary axillary dissection and thus to prevent iatrogenic morbidity. The main criticism of this procedure concerns the consequences of a false-negative biopsy. To date, no randomized controlled phase III clinical trials have been published, while multicentre studies evaluating the method's accuracy compared with complete axillary dissection are still in progress. There is extensive literature available on phase I–II studies that has confirmed the accuracy, feasibility and reliability of the sentinel node procedure[5,6]. There is now a need for quality control and long-term follow-up studies to provide data supporting the sentinel node procedure as an accurate staging method. To date, there are only two studies providing data on patients who had a sentinel lymph node dissection as a sole procedure[7,8]. Both studies, one with a median follow-up of 39 months and the other with less than 2 years' median follow-up, showed no local axillary recurrence in 67 and 285 patients respectively[7,8]. The present series confirms these results.

In their meta-analysis Fraile *et al.*[5] concluded that 'due to limitations of axillary lymph node dissection as the golden standard, sentinel node biopsy can in fact be considered a more accurate method for nodal staging'. Based on extensive reviews and meta-analyses of most of the existing phase I and II studies, the false-negative rate of the sentinel node biopsy (including completion axillary dissection) in breast cancer has been shown to vary between 0 and 17 per cent, with a mean of 8–9 (95 per cent confidence interval 7–11) per cent[5,6].

The sensitivity for the present patient population should have been least as high as a previously shown value of 95 per cent[3] because of the authors' tendency to perform an ultrasonographic investigation (with fine-needle aspiration) of the axilla when there are palpable axillary nodes[9]. By this means, patients with positive axillary nodes are selected who can be excluded from the sentinel node biopsy procedure. This policy, incorporated in 1998, may reduce the false-negative rate and could be the reason why in the present series of 143 patients the positive nodal rate (30 per cent) was less than that published previously (37 per cent)[3].

A 95 per cent sensitivity of the sentinel node procedure means that the expected number of patients with residual nodal involvement after a negative sentinel node biopsy without further axillary dissection is 3 per cent, when the a priori chance of a positive node is 40 per cent. Considering 1000 patients with breast cancer, 400 patients will be truly node positive while 600 will be truly node negative. Assuming a 95 per cent sensitivity, 20 of the 400 patients will not be discovered as being node positive and will wrongly be put in the group of 600 true-negative patients. Thus, of the 620 sentinel node-negative patients, 20 will be falsely negative. Therefore, with a sensitivity of 95 per cent, only 3 per cent (20 of 620) of the patients thought to be negative are truly node positive. When the a priori number of true node-positive patients is smaller, then the number of false negatives will also be smaller.

The present study shows that, after a median follow-up of 24 months, only one patient had axillary residual nodal disease, although this case had a disastrous outcome. Recently, de Boer *et al.*[10] showed that axillary recurrence after complete axillary dissection for invasive breast cancer occurred in 59 (1 per cent) of 4669 patients at a median interval of 2·6 years. From the NSABP-04 study it is known that three-quarters of patients with breast cancer develop their axillary recurrence within 2 years[11].

Based on the calculations above, approximately three of the 100 patients would be expected to become positive for axillary residual disease at some time. Fortunately, the present data are better than expected. This may be due to adjuvant treatment, which was given to half of the patients ($n = 52$) based on tumour-related factors according to recent guidelines[12,13], because of the policy of detection of positive axillary nodes by ultrasonography and fine-needle aspiration, or simply because the follow-up period is still too short.

On the other hand, from previous studies it is known that about 20 per cent of patients with breast cancer who receive no treatment of the axilla will develop an axillary relapse[11]. When the incidence of true-positive axillary nodal metastases is about 40 per cent, why then is the relapse rate only 20 per cent after even 10 years of follow-up? Possible explanations for this include the role of the biological behaviour of the tumour, the systemic adjuvant treatment given, the type of surgery and (local) breast radiation[2,7].

The patient questionnaire showed that the morbidity of the sentinel node biopsy procedure is minor. Only a few patients described pain in the axillary scar, or numbness or paraesthesia of the skin. None of the patients developed oedema and only two patients responded that they had to change their hobbies or sports because of the operation in the axilla. After a complete axillary dissection, 30 per cent of patients have some kind of disabling pain, 10–30 per cent develop arm oedema, up to 70 per cent have numbness and 30 per cent have some form of functional impairment[14–16]. In a recent study it was shown that more than 30 per cent of the patients needed physiotherapy after the axillary operation compared with none in the present group[17].

The key question that remains is whether or not it is acceptable to have one fatal recurrence of local axillary disease while avoiding 99 unnecessary axillary dissections. Reflecting on this, one should keep in mind the indications for adjuvant chemotherapy according to recent guidelines: a given therapy with its morbidity should be advised only when an absolute 10-year survival benefit of 5 per cent can be gained[12,13]. Implicitly, this means that it is thought acceptable not to treat 96 patients unnecessarily with chemotherapy if there are four or fewer 10-year survivors to be gained.

It is concluded that when strict criteria for the sentinel node procedure are adhered to, a negative histopathological sentinel node biopsy without further axillary dissection is a correct part of good clinical practice in the treatment of patients with breast cancer and may thus be considered to be the standard of care.

References

1 McMasters KM, Giuliano AE, Ross MI, Reintgen DS, Hunt KK, Byrd DR *et al.* Sentinel-lymph-node biopsy for breast cancer – not yet the standard of care. *N Engl J Med* 1998; **339:** 990–5.

2 Spillane AJ, Sacks NPM. Role of axillary surgery in early breast cancer: review of the current evidence. *Aust N Z J Surg* 2000; **70:** 515–24.

3 Roumen RMH, Valkenburg JGM, Geuskens LM. Lymphoscintigraphy and feasibility of sentinel node biopsy in 83 patients with primary breast cancer. *Eur J Surg Oncol* 1997; **23:** 495–502.

4 Borgstein PJ, Meijer S, Pijpers R. Intradermal blue dye to identify sentinel lymph-node in breast cancer. *Lancet* 1997; **349:** 1668–9.

5 Fraile M, Rull M, Julian FJ, Fuste F, Barnadas A, Llatjos M *et al.* Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: an approach to its validity. *Ann Oncol* 2000; **11:** 701–5.

6 Sandrucci S, Casalegno PS, Percivale P, Mistrangelo M, Bombardieri E, Bertoglio S. Sentinel lymph node mapping and biopsy for breast cancer: a review of the literature relative to 4791 procedures. *Tumori* 1999; **85:** 425–34.

7 Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W *et al.* Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol* 2000; **18:** 2553–9.

8 Veronesi U, Galimberti V, Zurrida S, Pigatto F, Veronesi P, Robertson C *et al.* Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer. *Eur J Cancer* 2001; **37:** 454–8.

9 Bonnema J, van Geel AN, van Ooijen B, Mali SP, Tjiam SL, Henzen-Logmans SC *et al.* Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: new diagnostic method. *World J Surg* 1997; **21:** 270–4.

10 de Boer R, Hillen HFP, Roumen RMH, Rutten HJT, van der Sangen MJC, Voogd AC. Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer. *Br J Surg* 2001; **88:** 118–22.

11 Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL *et al.* Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985; **312:** 674–81.

12 Bontenbal M, Nortier JWR, Beex LVAM, Bakker P, Hupperets PSGJ, Nooij MA *et al.* Adjuvant systemic therapy for patients with resectable breast cancer: guideline from the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology. *Ned Tijdschr Geneeskd* 2000; **144:** 984–9.

13 Steering Committee on Clinical Practice Guidelines for the

Care and Treatment of Breast Cancer. Adjuvant systemic therapy for women with node-negative breast cancer. *CMAJ* 1998; **158**(Suppl 3): s43–51.

14 Liljegren G, Holmberg L. Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I. Results from a randomised trial. Uppsala–Orebro Breast Cancer Study Group. *Eur J Cancer* 1997; **33**: 193–9.

15 Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. *Br J Cancer* 1992; **66**: 136–8.

16 Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. *J Clin Oncol* 1999; **17**: 143–9.

17 Dons IPM, Stiegelis HE, Voogd AC, Coebergh JWW, Crommelin MA, Roumen RMH *et al.* Kwaliteit van leven na okselklierdissectie bij patienten met mammacarcinoom. *Ned Tijdschr Heelkd* 1998; **7**: 189–94.

If you wish to comment on this, or any other article published in the *BJS*, please visit the on-line correspondence section of the website (www.bjs.co.uk). Electronic communications will be reviewed by the Correspondence Editor and a selection will appear in the correspondence section of the Journal. Time taken to produce a thoughtful and well written letter will improve the chances of publication in the Journal.

Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer

L. Bergkvist, J. Frisell*, G. Liljegren†, F. Celebioglu*, S. Damm‡ and M. Thörn§

Department of Surgery and Centre for Clinical Research Uppsala University and ‡Department of Clinical Physiology and Nuclear Medicine, Central Hospital, Västerås, *Department of Surgery, Huddinge University Hospital, Stockholm, †Department of Surgery and Centre for Assessment of Medical Technology, University Hospital, Örebro and §Department of Surgery, Uppsala University Hospital, Uppsala, Sweden

Correspondence to: Dr L. Bergkvist, Department of Surgery and Centre for Clinical Research, Central Hospital, SE-72189 Västerås, Sweden (e-mail: leif.bergkvist@ltvastmanland.se)

Background: Sentinel node biopsy has recently evolved as a means of staging the axilla in breast cancer with minimal surgical trauma. The aim of this prospective multicentre study was to identify factors that influencd the detection and false-negative rates during the learning phase.

Methods: Data on all 498 sentinel node biopsies performed between August 1997 and December 1999 in Sweden were collected.

Results: A sentinel node was found in 450 patients (90 per cent). Preoperative scintigraphy visualized 83 per cent of all sentinel nodes. The detection rate was higher with same-day injection of tracer than with injection the day before (96 *versus* 86 per cent; $P < 0{\cdot}01$). Dye injected less than 5 min or more than 30 min before the start of the operation lowered the detection rate (less than 60 per cent *versus* more than 65 per cent; $P = 0{\cdot}02$). The detection rate varied from 61 to 100 per cent between surgeons. The false-negative rate was 11 per cent. The presence of multiple tumour foci and a high S-phase fraction increased the risk of a false-negative sentinel node, whereas the number of operations performed by each surgeon was less important.

Conclusion: Training of the individual surgeon influenced the detection rate, as did timing of tracer and dye injection. The false-negative rate seemed to be related to biological factors.

Paper accepted 20 August 2001

British Journal of Surgery 2001, **88**, 1644–1648

Introduction

Axillary lymph node dissection has long been the standard surgical procedure as part of treatment for invasive breast cancer. The presence or absence of axillary metastases is still the single most powerful predictor of outcome, despite the availability of numerous other biological and genetic markers[1,2]. Careful axillary dissection is also therapeutic[3]. Axillary dissection, however, is accompanied by considerable morbidity and there is a correlation between the number of nodes excised and the severity of postoperative discomfort[4,5].

Sentinel node biopsy has been developed during recent years to stage the axilla. The status of the sentinel node predicts the status of the rest of the nodes in the node basin[6–13]. Three different methods have been used to identify the sentinel node in patients with breast cancer: vital blue dye[7], lymphoscintigraphy with intraoperative use of a γ probe[6,9] and a combination of these two methods[8]. There is a learning curve, and every new surgeon who starts doing sentinel node biopsies needs training[11].

The technique of sentinel node biopsy was introduced in Sweden in 1997 and a pilot series was performed in three hospitals before the method was extended to other hospitals[14]. All surgeons who started doing sentinel node biopsies either visited one of these hospitals or attended a formal course to learn the technique. All patients who had a sentinel node biopsy in Sweden during the study interval were reported to the study coordinator and included in this analysis. The aim of this prospective multicentre study was to identify factors that influenced the rate of detection of the sentinel node, and factors that affected the false-negative rate during the learning phase.

Patients and methods

Data were collected on all 498 patients from 17 participating hospitals in Sweden in whom the sentinel node biopsy technique was used between August 1997 and December 1999. A standard protocol was used which was approved by the ethics committees in all regions. Eligible patients were those with an operable unifocal breast cancer (T_1–T_3) without suspicious palpable lymph nodes in the axilla, who were scheduled to have an operation that included axillary dissection. Patients with multicentric or multifocal tumours on preoperative mammography were excluded, as were those who had previously undergone breast biopsy or who had received preoperative radiotherapy or systemic therapy.

Lymphoscintigraphy

Preoperative lymphoscintigraphy was performed either on the same day as the operation, or the day before. The maximum interval between isotope injection and the start of the operation was 27 h. Injection of a ^{99m}Tc-radiolabelled colloid (Solco Nanocoll® or Albures®; Nycomed, Amersham, UK) at a dose of 40 MBq was done either around the tumour, subcutaneously or intradermally. Static images were obtained immediately after injection and then after approximately 60 min. If a sentinel node was not identified, another image was taken after 2 or 3 h. Imaging techniques may have varied between centres.

Operative technique

Immediately before the operation, 1 ml of a blue vital dye (Patent Blue V®; Guerbet, Paris, France) was injected around the tumour, subcutaneously or intradermally. A hand-held probe was used for intraoperative detection (Navigator®; USS Corporation, Norwalk, Connecticut, USA, Neo-Probe®; Neoprobe Corporation, Dublin, Ohio, USA, C-Trac®; Care Wise Medical Products, Morgan Hill, California, USA, Europrobe®; Eurorad, Sevres, France or Crystal Probe®; Nuclear Fields System, Des Plaines, Illinois, USA). The operation started with a small incision over the area with a hotspot in the axilla. By careful dissection the blue-stained lymphatics were sought and followed to a blue node. The probe was used to confirm that the node also contained radioactivity, or to guide the surgeon when no blue lymphatics were identified. Sentinel nodes thus identified were labelled and sent separately to the pathologist. Thereafter a level I and II axillary dissection was performed for validation of the sentinel node procedure.

Histopathology

The sentinel node was bisected if larger than 4 mm, and each part was embedded and sectioned separately. The sections were examined with routine haematoxylin and eosin or Van Gieson staining. If no cancer was detected with routine staining, a further two to three sections were examined after staining both with haematoxylin and eosin or Van Gieson and immunohistochemically with cytokeratin antibodies. The type of antibodies used varied between laboratories. The remaining axillary dissection specimen (excluding the sentinel node) was examined using routine staining.

Definitions

A blue node or a node with radioactivity (or both) was defined as a sentinel node. No specific ratio between the hot node and background radioactivity was defined. Detection rates were presented as the proportion of operations performed by an individual surgeon in which the sentinel node was found, divided by the total number of operations performed by the same surgeon. False-negative rates were calculated as the number of patients in whom the sentinel node was negative but another lymph node in the axilla contained metastases, divided by the total number of patients with a positive axilla.

Statistical analysis

For comparison of detection and false-negative rates, χ^2 analyses were performed. All *P* values were two-tailed. Ninety-five per cent confidence intervals (c.i.) were calculated for detection rates within ranges of numbers of operations, based on the assumption of a binomial distribution. Initially all analyses performed were univariate. Variables found to have a statistically significant influence on the false-negative rate were included in a multiple logistic regression model.

Results

Overall, data from 498 patients were collected from 17 hospitals, and 28 different surgeons participated in the study. The size of the invasive tumour ranged from 1 to 100 (mean 20, median 18) mm. The majority (80 per cent) of the patients had breast-conserving surgery and 40 per cent had axillary lymph node metastases. The median number of sentinel nodes retrieved was 2·0 (range 1–9) and the median number of non-sentinel nodes was 10·5 (range 0–33). In 56 per cent of the patients the isotope injection was made subcutaneously or subdermally, in 27 per cent around the tumour, in 9 per cent with a combined technique and in 3 per cent intradermally. Corresponding percentages for dye injection were 73, 14, 3 and 4 per cent respectively. In 5 per cent of isotope injections and 6 per cent of dye injections information on the depth of injection was missing.

Sentinel node detection

A sentinel node was identified in 90 per cent of all patients. Preoperative lymphoscintigraphy disclosed at least one sentinel node in 83 per cent of the patients. Thirty-nine per cent (32 of 82) of the sentinel nodes not seen on lymphoscintigraphy could be identified using the γ probe during axillary exploration, whereas 8 per cent (31 of 403) of those seen on scintigraphy were not detected with the probe. The overall detection rate using the probe alone was 84 per cent compared with 67 per cent using the dye alone. According to the protocol, the combination of dye and isotope should have been used, but this occurred in only 465 patients. Reasons for not using the combined method included lack of dye or isotope among the first patients treated in some centres. Among patients in whom the sentinel node was detected, it was found by both methods in 66 per cent, with the probe alone in 26 per cent and with the dye alone in 8 per cent.

Timing of injections

Forty-eight per cent of the patients received the isotope injection on the same day as the operation, and 52 per cent the day before. The detection rate was higher in those who had the isotope injection on the same day (96 per cent) than in those who received it the day before (86 per cent) ($P < 0\cdot01$). Identification with the γ probe was successful in 90 per cent when the isotope was given on the same day, but in only 77 per cent when it was given the previous day ($P < 0\cdot01$).

Visual identification of the sentinel node was possible in over 65 per cent of the patients when the dye was injected more than 5 min but less than 30 min before the start of the operation. If this time was less than 5 min or more than 30 min, fewer than 60 per cent of the nodes were seen ($P = 0\cdot02$). The injection technique, i.e. whether the dye was injected subcutaneously, around the tumour or intradermally, was of marginal importance.

Age of the patient

There was a trend, although not statistically significant, towards a lower detection rate with increasing patient age. In women under 50 years of age the detection rate was 95 per cent, in patients aged 50–69 years it was 90 per cent, and in those older than 70 years it was 87 per cent ($P = 0\cdot12$).

Training

The most important factor that affected the sentinel node detection rate was the individual surgeon. Detection rates varied between 61 and 100 per cent for different surgeons. The number of operations performed had less influence on the detection rate, with respect to both the whole group of surgeons and the individual surgeon (*Table 1*). After 30 operations the detection rate was over 90 per cent for the whole group.

False-negative rate

The overall false-negative rate was 11 per cent (20 of 184) (*Table 2*). When only routine staining was used, 304 sentinel node biopsies were classified as negative. In 18 of these patients, however, metastases were detected using immunohistochemical staining. The conversion rate using immunohistochemistry was therefore 6 per cent (18 of 304). Of the 18 patients with sentinel nodes that were positive only immunohistochemically, 15 had no other involved nodes in the axilla.

Three factors affected the false-negative rate in the univariate analysis: the hospital at which the operation had been performed, the S-phase fraction (cut-off point 10 per cent) (low S-phase 6 per cent *versus* high S-phase 20 per cent; $P = 0\cdot01$) and the presence of multiple foci (unifocal tumours 9 per cent *versus* multifocal 33 per cent; $P < 0\cdot01$).

Table 1 Sentinel node detection rate by number of operations performed by each surgeon

No. of operations	No. of operations in the range	Detection rate
1–10	167	86 (84–89)
11–20	117	95 (93–98)
21–30	55	87 (83–92)
31–40	41	91 (87–96)
41–50	29	97 (93–100)
> 50	41	93 (89–97)

Values in parentheses are 95 per cent confidence intervals. Calculation of the 95 per cent confidence interval was based on the assumption of a binomial distribution. $P = 0\cdot10$ for difference between the strata

Table 2 Cross-tabulation of the number of positive and negative sentinel nodes against axillary involvement with tumour

	Axillary node status		
	Positive	Negative	Total
Sentinel node Positive	164	0	164
Negative	20	266	286
Total	184	266	450

False-negative rate 11 per cent (20 of 184); sensitivity 89 per cent (164 of 184); specificity 100 per cent (0 of 266); negative predictive value 93 per cent (266 of 286); overall accuracy 96 per cent (430 of 450)

Multifocal tumours were those in which pathological examination revealed foci of tumour tissue at some distance from the original tumour that were not seen on preoperative mammography. Only the S-phase fraction and presence of multiple tumour foci remained statistically significant risk factors for a false-negative sentinel node biopsy in a multiple logistic regression model (odds ratio (95 per cent c.i.) 9·5 (1·7–52·9) and 5·6 (1·6–20·0) respectively). Neither the technique of the individual surgeon, the number of operations, nor the injection technique or timing of injections influenced the false-negative rate. The false-negative rate was not affected by other biological tumour factors such as location of the tumour, patient's age, oestrogen receptor status, Elston grade, tumour type or size, or the presence of an extensive intraductal component in close relation to the invasive cancer.

Discussion

The majority of surgeons reached an acceptable level of sentinel node detection after a few training operations, but there was considerable variation that remained irrespective of the number of operations performed. This observation agreed with the findings of Krag *et al.*[11] that the detection rate varied from 79 to 98 per cent for different surgeons. However, in that study there was also an effect of quantitative training, which was not so clear in the present study. It is difficult to define a level after which the surgeon and the organization at the hospital are judged to be ready to do sentinel node biopsy as a single staging, but the detection rate after 30 operations was consistently over 90 per cent. This level has been chosen in Sweden for future study participation.

Another factor that influenced the detection rate was the use of both dye and isotope. If dye alone had been used, the failure rate would have been 33 per cent. This conforms with the first publication of Guiliano *et al.*[7] in which a 35 per cent failure rate was reported with dye alone. In later publications from the same group, much higher rates of detection were reported[10]. In Sweden, the combined approach is advocated as agreed by many others[8,12,15]. The timing of the isotope and dye injections also influenced the results. A higher detection rate was observed when the isotope was given on the day of the operation. This was probably due to its short half-life (6 h). When it was injected the day before the operation, less than 13 per cent of the initial isotope count remained, making detection with the probe more difficult. In most cases 40 MBq of technetium was used, which might be too low a dose. Increasing the dose to 60 or 80 MBq might facilitate the identification in future. For best results the blue dye should be injected between 5 and 30 min before surgery. In this study the injection technique, i.e. subcutaneous, around the tumour or intradermally, did not influence the identification rate. All routes of injection seem to work, but a prospective randomized study is needed to establish which technique is best. There is a difference, however, in the identification of parasternal nodes, which seems to be dependent on the site of injection. In the present study the incidence of parasternal nodes was 6 per cent on preoperative lymphoscintigraphy; this was lower than that in a series from the Netherlands Cancer Institute (19 per cent), where an intratumour injection was used[16]. When more superficial techniques have been used hardly any involved parasternal nodes have been identified[17]. The importance of detecting parasternal nodes, however, remains to be clarified.

The value of preoperative lymphoscintigraphy has been questioned by some authors[18]. In the present study the localization of a hotspot on lymphoscintigraphy facilitated the identification of the sentinel node by the probe. In almost 40 per cent of patients with no hotspot on lymphoscintigraphy, however, a hot node was found with the probe at operation. The majority of these patients had laterally or centrally located tumours. Inadequate imaging might have contributed to this finding, probably due to overshining from the injection site in the axilla on the scintigram. Among patients with a hotspot seen at preoperative scintigraphy, no sentinel node was found at all in almost 8 per cent. Perhaps these would have been identified at operation had the surgeon been a little more experienced or a little more patient.

The false-negative rate in this study was 11 per cent. This is in line with other reports[11,12], especially when the learning procedures were included in the series. The data did not indicate that false-negative sentinel nodes were more frequent in the first part of the series; false negatives were scattered across the whole series of patients, and among all surgeons. Two factors predicted a false-negative finding, namely a high S-phase fraction and a multifocal tumour. To the authors' knowledge, the S-phase fraction has not been studied before, and the importance of this finding cannot therefore be determined. Greater biological aggressiveness among these tumours might contribute to the false-negative rate, but there was no clear relation with the Elston grade or tumour size, which are also supposed to reflect biological growth characteristics. Multifocal tumours were not found to influence false-negative rate in a small series by Schrenk and Wayand[19], but they used a subareolar injection technique and the series included only ten positive axillas.

The strength of this study lies in the fact that all operations from every hospital and every surgeon that has started to use the sentinel node procedure in Sweden were collected. It was not just the work of dedicated pioneers. The study thus gives a picture of what happens when this method is implemented widely. The participating departments ranged from university hospitals and large county hospitals to small community hospitals. Despite this diversity, the overall results were acceptable, with a detection rate of over 90 per cent and a false-negative rate comparable to that in other studies. A possible limitation of the study is that the handling of sentinel node specimens in different pathology departments might have varied. No pathological review has been performed. Furthermore, the imaging technique was not standard and differed between departments of nuclear medicine.

These results indicate that the personal skill of a surgeon is essential to the detection rate, and that the use of the combined isotope and dye injection technique and the timing of the isotope and dye injections are also of great importance.

Acknowledgements

Participating hospitals (in alphabetical order) and respective surgeons on behalf of whom this paper was prepared were: Borås Hospital (T. Ramhult and L. Rex); Danderyd Hospital, Stockholm (C. Wadström); Falun Hospital (A. Cohen and G. Christensen); Helsingborg Hospital (P. E. Jönsson); Huddinge University Hospital, Stockholm (J. Frisell, F. Celebiolgu and L. Perbeck); Karolinska Hospital, Stockholm (K. Sandelin); Karlstad Hospital (T. Jahnberg and B. Nilsson); University Hospital Linköping (L. G. Arnesson); University Hospital Lund (C. Ingvar, A. Bergenfelz and J. Kaij); University Hospital MAS, Malmö, (P. E. Jönsson); Sahlgrenska University Hospital, Mölndal, (J. Mattsson); Säffle Hospital (H. Sällström); Södersjukhuset, Stockholm (J. Frisell); University Hospital Umeå (S. Emdin and A. Boström); University Hospital Uppsala (M. Thörn and F. Wärnberg); Västerås Hospital (L. Bergkvist, A. Helleberg, P. Gustafsson and A. Chabok); Växjö Hospital (T. Ambré); University Hospital, Örebro (G. Liljegren).

References

1 Chadha M, Chabon AB, Friedman P, Vikram B. Predictors of axillary lymph node metastases in patients with T_1 breast cancer. A multivariate analysis. *Cancer* 1994; **73:** 350–3.
2 Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer: a review. *Cancer* 1995; **76:** 1491–512.
3 Moffat FL, Senofsky GM, Davis K, Clark KC, Robinsson DS, Ketcham AS. Axillary node dissection for early breast cancer: some is good, but all is better. *J Surg Oncol* 1992; **51:** 8–13.
4 Liljegren G, Holmberg L, Uppsala–Örebro Breast Cancer Study Group. Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I. Results from a randomised trial. *Eur J Cancer* 1997; **33:** 193–9.
5 Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. *Br J Cancer* 1992; **66:** 136–8.
6 Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993; **2:** 335–40.
7 Guiliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; **220:** 391–401.
8 Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N *et al.* Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996; **276:** 1818–22.
9 Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bodoni M *et al.* Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997; **349:** 1864–7.
10 Guiliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997; **15:** 2345–50.
11 Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Schriver C *et al.* The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med* 1998; **339:** 941–6.
12 O'Hea BJ, Hill ADK, El-Shirbiny AM, Yeh SDJ, Rosen PP, Coit DG *et al.* Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan–Kettering Cancer Center. *J Am Coll Surg* 1998; **186:** 423–7.
13 Hill AD, Tran KN, Akhurst T, Yeung H, Yeh SD, Rosen PP *et al.* Lessons learned from 500 cases of lymphatic mapping for breast cancer. *Ann Surg* 1999; **229:** 528–35.
14 Frisell J, Bergkvist L, Liljegren G, Thörn M, Damm S, Rydman H *et al.* Sentinel node in breast cancer – a Swedish pilot study of 75 patients. *Eur J Surg* 2001; **167:** 179–83.
15 Cox CE, Pendas S, Cox JM, Joseph E, Shons AR, Yeatman T *et al.* Guidelines for sentinel node biopsy and lymphatic mapping of patients with breast cancer. *Ann Surg* 1998; **227:** 645–53.
16 Jansen L, Doting MH, Rutgers EJ, de Vries J, Olmos RA, Nieweg OE. Clinical relevance of sentinel lymph nodes outside the axilla in patients with breast cancer. *Br J Surg* 2000; **87:** 920–5.
17 Veronesi U. The sentinel node and breast cancer. *Br J Surg* 1999; **86:** 1–2.
18 McMasters KM, Guiliano AE, Ross MI, Reintgen DS, Hunt KK, Byrd DR *et al.* Sentinel-lymph-node biopsy for breast cancer – not yet the standard of care. *N Engl J Med* 1998; **339:** 990–5.
19 Schrenk P, Wayand W. Sentinel-node biopsy in axillary lymph-node staging for patients with multicentric breast cancer. *Lancet* 2001; **357:** 122 (Letter).

Original article

Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery

T. M. Farrell, W. S. Richardson, T. L. Trus, C. D. Smith and J. G. Hunter

Department of Surgery, Emory University School of Medicine, Atlanta, Georgia, USA
Correspondence to: Dr T. M. Farrell, Department of Surgery, Campus Box 7210, University of North Carolina, Chapel Hill, North Carolina 27599-7210, USA (e-mail tfarrell@med.unc.edu)

Background: Atypical manifestations of gastro-oesophageal reflux (GOR) include asthma, chest pain, cough and hoarseness. The effectiveness of antireflux surgery for these symptoms is uncertain. The present study compared symptomatic response rates for typical and atypical GOR symptoms after fundoplication.

Methods: Between October 1991 and January 1998, 324 patients underwent laparoscopic fundoplication at Emory University Hospital and returned postoperative questionnaires. Severity of typical (heartburn) and atypical (asthma, chest pain, cough and hoarseness) GOR symptoms was reported by patients on a 0–4 scale before surgery, and at 6 and 52 weeks after operation. Patients were stratified based on preoperative symptoms into three groups: group 1 (severe heartburn/minimal atypical symptoms), group 2 (severe heartburn/severe atypical symptoms) and group 3 (minimal heartburn/severe atypical symptoms).

Results: In group 1 ($n = 173$) heartburn improved in 99 per cent and resolved in 87 per cent. In group 2 ($n = 95$) heartburn improved in 95 per cent and resolved in 76 per cent, and atypical symptoms improved in 94 per cent and resolved in 42 per cent. In group 3 ($n = 56$) atypical symptoms improved in 93 per cent and resolved in 48 per cent. Although all symptoms were improved by fundoplication, resolution was more likely for heartburn than for atypical symptoms.

Conclusion: Atypical symptoms of GOR are improved by fundoplication, but symptom resolution occurs in fewer than 50 per cent of patients.

Paper accepted 22 August 2001

British Journal of Surgery 2001, 88, 1649–1652

Introduction

Recently, there has been a great deal of interest in the evaluation and management of atypical symptoms of gastro-oesophageal reflux (GOR)[1–6]. While antireflux surgery manages the typical symptoms of GOR (heartburn and regurgitation) effectively, there is limited information regarding its value for atypical GOR symptoms (asthma, chest pain, cough and hoarseness)[2,7,8]. Several small studies have reported resolution of atypical GOR symptoms with intensive antisecretory therapy, but these studies lacked appropriate controls[3–6]. In the authors' series, it was found that fundoplication decreased the need for systemic corticosteroids among asthmatic patients with GOR[9].

In the present report, the effect of laparoscopic antireflux surgery on atypical GOR symptoms was investigated.

Patients and methods

Between October 1991 and January 1998, 324 patients who underwent laparoscopic fundoplication completed preoperative and postoperative symptom questionnaires. Preoperative symptom severity scores (SSS) for typical symptoms (heartburn) and atypical symptoms (asthma, chest pain, cough and hoarseness) were reported by all patients. Symptom scores ranged from 0 (none) to 4 (incapacitating). Preoperative evaluation included oesophageal manometry and endoscopy in all patients, and ambulatory oesophageal pH monitoring and gastric function testing in selected patients[10]. Ambulatory pH assessment was omitted in approximately 20 per cent of patients who presented with severe heartburn but also had evidence of severe oesophageal ulceration or Barrett's oesophagus.

Three patient groups were defined based on the preoperative symptom severity. Patients in group 1 had severe heartburn (SSS 3–4) but minimal atypical symptoms (SSS 0–2). Those in group 2 had severe heartburn (SSS 3–4) and one or more severe atypical symptoms (SSS 3–4). Patients in group 3 had minimal heartburn (SSS 0–2) and one or more severe atypical symptoms (SSS 3–4). The operative technique has been described previously[7].

Postoperative symptom severity scores are obtained routinely at 6 and 52 weeks in the authors' practice. One-year postoperative data, typically obtained by mail, were available for 211 patients. For 113 patients 6-week data from the first postoperative clinic visit were utilized either because the patients had not reached the 1-year point at the time of the study or had failed to return the second survey. Overall, 5 per cent of possible patients were excluded because of the lack of any postoperative symptom scores owing to data transfer errors or lack of follow-up.

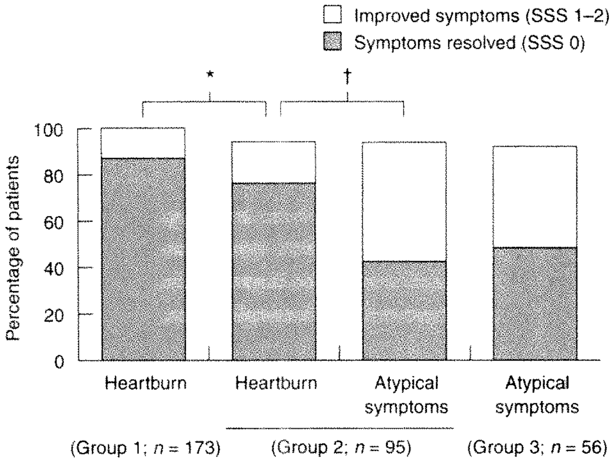


Fig. 1 Comparison of symptom response after laparoscopic fundoplication in patients in group 1 (severe heartburn only), group 2 (severe heartburn and severe atypical symptoms) and group 3 (severe atypical symptoms only). *$P < 0{\cdot}05$ (Wilcoxon rank sum test); †$P < 0{\cdot}01$ (Wilcoxon signed rank test). SSS, symptom severity score

When two or more atypical symptoms were rated severe (SSS 3) or incapacitating (SSS 4) before operation, the mean of the corresponding postoperative symptom scores was used to compare aggregate symptom response in the defined groups (*Fig. 1*). Continuous variables (age, oesophageal pH and manometric data) were compared among the three groups by analysis of variance. Ordinal data (symptom severity scores) were compared between groups with the Wilcoxon rank sum test. Ordinal data for different symptoms were compared within groups with the Wilcoxon signed rank test. $P < 0{\cdot}05$ was considered statistically significant.

Results

One hundred and seventy-three patients met the criteria for group 1, 95 patients for group 2 and 56 for group 3. Patients who presented with atypical symptoms (groups 2 and 3) were slightly older than those with heartburn alone (*Table 1*). Ambulatory pH studies demonstrated significant differences in the quantity of acid reflux between groups, with group 1 greater than group 2, and group 2 greater than group 3. Oesophageal motility was similar between the three groups.

Overall, 296 of 324 patients reported improvement or resolution of severe GOR symptom(s) (*Fig. 1*). In group 1 99 per cent had an improvement in heartburn (87 per cent resolution), in group 2 95 per cent had an improvement in heartburn (76 per cent resolution) and 94 per cent had an improvement in atypical symptoms (42 per cent resolution), and in group 3 93 per cent had an improvement in atypical symptoms (48 per cent resolution). The improvement in heartburn was significantly better for patients in group 1

Table 1 Demographic and diagnostic variables of 324 patients who had laparoscopic fundoplication

	Group 1	Group 2	Group 3	P*
No. of patients	173	95	56	
Sex ratio (M : F)	107 : 66	46 : 49	24 : 32	
Age (years)	46(14)	50(12)	50(14)	< 0·05
pH less than 4·0				
Total time (min)	16·9(10·5)	14·6(9·0)	11·4(8·3)	< 0·05
Supine time (min)	15·9(14·5)	11·0(10·4)	9·3(11·6)	< 0·05
Lower oesophageal sphincter pressure (mmHg)	11·6(7·9)	14·2(10·4)	14·5(8·5)	n.s.
Mean distal oesophageal body pressure (mmHg)	80·0(33·6)	85·3(34·3)	86·7(36·1)	n.s
Percentage of wet swallows with normal peristalsis	87·3(21·9)	89·4(17·1)	86·4(23·8)	n.s.

Values are mean(s.d.). n.s., Not significant. *Analysis of variance

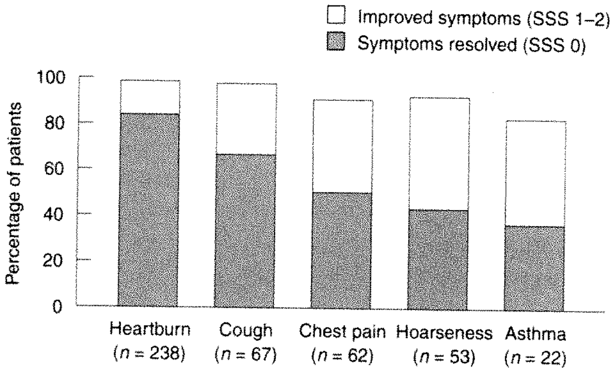


Fig. 2 Symptom response to laparoscopic fundoplication in patients with severe preoperative symptoms (symptom severity score (SSS) 3–4)

than for those in group 2 ($P < 0{\cdot}05$), principally because of the higher proportion of patients reporting complete resolution. The response of atypical symptoms in patients in group 2 was similar to that reported by patients in group 3 ($P = 0{\cdot}54$). Among patients in group 2, the improvement in heartburn exceeded the improvement in atypical symptom response, again as a consequence of the greater ratio of complete to partial response.

Of 20 patients with oesophageal symptoms and eight patients with atypical symptoms who reported no improvement or worsened symptoms after fundoplication, none had oesophageal dysmotility on preoperative manometry.

Fig. 2 demonstrates the relative impact of fundoplication on all severe (SSS 3–4) GOR symptoms. Heartburn was by far the most responsive symptom, with 97 per cent improvement (83 per cent resolution). Conversely, asthma was the least responsive, with 82 per cent improvement (36 per cent resolution).

Discussion

The differential diagnosis of non-cardiac chest pain includes occult cardiac disease (microvascular angina), musculoskeletal discomfort, psychological problems and oesophageal disease (oesophageal spasm and GOR)[11]. In previous series, chest pain believed to be the result of GOR improved in half of patients treated, but resolution was unpredictable[2,12–15]. In the present study, chest pain improved in 90 per cent of patients following laparoscopic fundoplication, with symptom resolution in 50 per cent of patients. Improved outcomes resulted from strict adherence to preoperative diagnostic testing protocols (endoscopy, manometry and 24-h pH monitoring) and the protection from reflux offered by laparoscopic fundoplication.

Medical therapy is variably effective for GOR-associated asthma, cough or hoarseness, and symptom resolution is uncommon[3–6,16–18]. Asthmatics may have several 'triggers' for bronchospasm in addition to GOR[19], and may have heightened sensitivity to oesophageal acid[20]. Patients with hoarseness suffer primary laryngeal injury from refluxed gastric acid[21]; however, secondary injury from excessive voice clearing and coughing may contribute to symptoms. Occasionally, upper oesophageal sphincter dysfunction may increase the occurrence of hypopharyngeal acid reflux[22,23]. Finally, chronic laryngeal or tracheobronchial injury may not be reversed completely by elimination of reflux[24].

DeMeester *et al.* reported a 70 per cent incidence of occult GOR among patients with chronic respiratory symptoms, but found that only a minority was helped by antireflux surgery[2]. So *et al.*[15] reported response rates of 58 and 78 per cent for pulmonary and laryngeal symptoms respectively. Chen and Thomas[25] found that atypical symptoms were improved in only half of patients. In contrast to these discouraging reports, 93 per cent of the patients with severe atypical symptoms in the present study reported symptom improvement and 48 per cent responded completely to antireflux surgery.

Johnson and colleagues[26] reported that patients with oesophageal dysmotility were more likely to have persistent respiratory symptoms after surgery, but did not report the severity of these symptoms before or after operation. Knight *et al.*[27] reported that 73 per cent of patients with atypical GOR had evidence of oesophageal dysmotility. In the present series, all patients with severe respiratory symptoms and documented poor oesophageal peristalsis reported improvement or resolution of atypical symptoms after fundoplication that was equal to, or better than, that reported by patients with atypical symptoms and normal preoperative manometry.

It appears that laparoscopic antireflux surgery is extremely effective at improving atypical GOR symptoms, but only about half of patients with severe symptoms will achieve a complete response.

References

1 Richter JE. Typical and atypical presentations of gastroesophageal reflux disease. The role of esophageal testing in diagnosis and management. *Gastroenterol Clinic North Am* 1996; **25:** 75–102.
2 DeMeester TR, Bonavina L, Iascone C, Courtney JV, Skinner DB. Chronic respiratory symptoms and occult gastroesophageal reflux. A prospective clinical study and results of surgical therapy. *Ann Surg* 1990; **211:** 337–45.
3 Stahl WG, Beton RR, Johnson CS, Brown CL, Waring JP.

Diagnosis and treatment of patients with gastroesophageal reflux and noncardiac chest pain. *South Med J* 1994; **87:** 739–42.

4 Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW, Bradley LA. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; **100:** 395–405.

5 Waring JP, Lacayo L, Hunter J, Katz E, Suwak B. Chronic cough and hoarseness in patients with severe gastroesophageal disease: diagnosis and response to therapy. *Dig Dis Sci* 1995; **40:** 1093–7.

6 Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med* 1994; **96:** 321–6.

7 Hunter JG, Trus TL, Branum GD, Waring JP, Wood WC. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. *Ann Surg* 1996; **223:** 673–85.

8 Hinder RA, Filipi CJ, Wetscher G, Neary P, DeMeester TR, Perdikis G. Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease. *Ann Surg* 1994; **220:** 472–83.

9 Spivak H, Smith CD, Phichith A, Galloway K, Waring JP, Hunter JG. Asthma and gastroesophageal reflux: fundoplication decreases need for systemic corticosteroids. *J Gastrointest Surg* 1999; **3:** 477–82.

10 Waring JP, Hunter JG, Oddsdottir M, Wo J, Katz E. The preoperative evaluation of patients considered for laparoscopic antireflux surgery. *Am J Gastroenterol* 1995; **90:** 35–8.

11 Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. *Ann Surg* 1994; **220:** 137–45.

12 Richter JE. Overview of diagnostic testing for chest pain of unknown origin. *Am J Med* 1992; **92:** 41–5S.

13 Achem SR, Kolts BE, Wears R, Burton L, Richter JE. Chest pain associated with nutcracker esophagus: a preliminary study of the role of gastroesophageal reflux. *Am J Gastroenterol* 1993; **88:** 187–92.

14 Singh S, Richter JE, Hewson EG, Sinclair JW, Hackshaw BT. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. *Ann Intern Med* 1992; **117:** 824–30.

15 So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. *Surgery* 1998; **124:** 28–32.

16 DeMeester TR, O'Sullivan GC, Bermudez G, Midell AI, Cimchowski GE, O'Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann Surg* 1982; **196:** 488–98.

17 Harper PC, Bergner A, Kaye MD. Antireflux treatment for asthma. Improvement in patients with associated gastroesophageal reflux. *Arch Intern Med* 1987; **147:** 56–60.

18 Larrain A, Carrasco E, Galleguillos F, Sepulveda R, Pope CE II. Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. *Chest* 1991; **99:** 1330–5.

19 Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest* 1993; **104:** 1511–17.

20 Irwin RS, Curley FJ, French CL. Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. *Chest* 1993; **103:** 1662–9.

21 Schan CA, Harding SM, Haile JM, Bradley LA, Richter JE. Gastroesophageal reflux-induced bronchoconstriction. An intraesophageal acid infusion study using state-of-the-art technology. *Chest* 1994; **106:** 731–7.

22 Delahunty JE, Cherry J. Experimentally produced vocal cord granulomas. *Laryngoscope* 1968; **78:** 1941–7.

23 Katz PO. Ambulatory esophageal and hypopharyngeal pH monitoring in patients with hoarseness. *Am J Gastroenterol* 1990; **85:** 38–40.

24 Shaker R, Mibrath M, Ren J, Toohill R, Hogan WJ, Li Q *et al.* Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. *Gastroenterology* 1995; **109:** 1575–82.

25 Chen RY, Thomas RJ. Results of laparoscopic fundoplication where atypical symptoms coexist with oesophageal reflux. *Aust N Z J Surg* 2000; **70:** 840–2.

26 Johnson WE, Hagen JA, DeMeester TR, Kauer WK, Ritter MP, Peters JH *et al.* Outcome of respiratory symptoms after antireflux surgery on patients with gastroesophageal reflux disease. *Arch Surg* 1996; **131:** 489–92.

27 Knight RE, Wells JR, Parrish RS. Esophageal dysmotility as an important co-factor in extraesophageal manifestations of gastroesophageal reflux. *Laryngoscope* 2000; **110:** 1462–6.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk*

Randomized study to examine the value of on-table inspection of the appendix mucosa (*Br J Surg* 2001; 88: 837–8)

Letter 1

Sir

It is not clear that the authors have provided a reliable answer to a practical intraoperative problem – is inflammation of the appendix secondary to other disease? As a first year registrar I operated on a patient and removed, as I expected, an inflamed and fibrin-covered appendix. Only after closing the abdomen did I open the appendix to be confronted by a normal mucosa. This required an explanation; the abdomen was reopened and exploration revealed an inflamed Meckel's diverticulum, which was removed. Thereafter, over 35 years, I made it the rule that the removed appendix should be placed in a sterile dish and opened with the tips of sterile scissors and forceps; after inspection the dish and contents were discarded. On a number of occasions this produced important information. Occasionally the opened empty perforated appendix showed where a faecalith had lain, so this had to be pursued in the wound. On other occasions the appendix mucosa was normal, so the source of the obvious serosal inflammation had to be sought in an adjacent viscus. I recognize that my experience is anecdotal, but it presents evidence of a real problem that is not solved by subsequent histological examination. Primary acute appendicitis is much more common than the secondary form, so it is valuable to have a quick and harmless method of identifying the occasional unusual case.

P. F. Jones
7 Park Road
Cults
Aberdeen AB15 9HR
UK

Letter 2

Sir

I disagree with the authors' conclusion that opening the appendix on-table should be discouraged. There are numerous, albeit rare, causes of acute appendicitis that can be identified by opening the appendix. This is particularly true in tropical countries where clinically important pathological findings have been found in 5 per cent of appendices[1]. Helminthiasis is still relatively frequent in many developing countries, and often mimics acute appendicitis. In addition, 0·9 per cent of specimens will harbour a tumour and over half of these will be carcinoids[2]. Opening surgical specimens could compromise histopathology methods if it is carried out incorrectly. Surgeons should therefore clarify with the pathology department the correct protocol for opening a specimen. I hope that trainee surgeons do not abandon the practice of examining surgically removed specimens based on the conclusions of this article.

Z. Soonawalla
Department of General Surgery
Morriston Hospital
Swansea SA6 6NL
UK

1 Gupta SC, Gupta AK, Keswani NK, Singh PA, Tripathi AK, Krishna V. Pathology of tropical appendicitis. *J Clin Pathol* 1989; **42:** 1169–72.
2 Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7970 appendectomies. *Dis Colon Rectum* 1998; **41:** 75–80.

Author's reply

Sir

Similar anecdotal evidence arises from our study and one patient whose appendix was opened was still labelled as having appendicitis despite the subsequent histological analysis revealing only serosal inflammation due to adjacent extra-appendiceal pathology. However, the purpose of this randomized prospective study was to refute or validate such anecdotes. The conclusion from our results was that, on balance, opening the appendix if anything increases the likelihood of a false positive diagnosis of appendicitis. The practical implications were that the surgical diagnosis of appendicitis is correct in those specimens that appeared severely inflamed but usually incorrect for those labelled mildly inflamed. For those patients with a mildly inflamed specimen, we suggest that, rather than opening the appendix (which may give false reassurance), it is more important to perform a thorough laparotomy.

Mr Soonawalla may be failing to distinguish between the practice of opening the appendix and the need for subsequent histological examination. It is the need for histological examination that is stressed in his first reference. Of those appendices that had clinically important pathological findings, the majority would not have become apparent until histological examination. Moreover, the detection of those potentially apparent at the time of removal, and this includes the important subgroup of carcinoid tumours, would not alter initial management. Further treatment is similarly dependent upon definitive histological examination.

G. Pettigrew
Department of Surgery
Level E9, Box 202
Addenbrooke's Hospital
Cambridge CB2 2QQ
UK

Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer (*Br J Surg* 2001; 88: 704–7)

Sir

The results of this study suggest that this colloid, subject to verification by others, could have an important role in sentinel node biopsy. For investigators in the UK, however, 'notes for guidance' issued by the Administration of Radioactive Substances Advisory Committee (ARSAC), specify a 'diagnostic reference level' of 40 MBq for the use of technetium-99m colloid in 'lymph node imaging'[1]. ARSAC is prepared to consider applications for use of increased doses in particular cases, if scientific justification can be given. The authors used between 37 and 185 MBq per patient. A number of successful studies of sentinel node biopsy have been conducted in the UK using 40 MBq or less of colloid (other than rhenium sulphide). It is unlikely that studies using such high doses would be sanctioned in the light of these results. However, prospective evaluation of lower doses of colloidal rhenium sulphide would yield valuable data pertinent to sentinel node biopsy in the UK.

C. Rogers
I. A. F. Azmy*
Department of Surgery
Rotherham District General Hospital
Rotherham S60 2UD
**The Royal Hallamshire Hospital*
Sheffield S10 2JF
UK

1 Administration of Radioactive Substances Advisory Committee. Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources, December 1998.

Author's reply

Sir

The optimal dose of radiotracer is one of the problems still to be solved in the technique of sentinel node biopsy. Most investigators use approximately 40 MBq of technetium-99m but others report a higher sentinel node identification rate with a high dose of radioactive tracer[1,2]. The problem lies in the fact that migration of radiocolloids varies from patient to patient and with the type of colloid used. It is impossible to predict the optimal dose before radiotracer injection.

We have performed sentinel node biopsy using 'high dose' (mean 125 MBq) rhenium colloid in 190 patients and the sentinel node was identified in all cases, but a combination of low dose (14·8–74 MBq) rhenium and blue dye showed an insufficient sentinel node identification rate of 96 per cent[3].

In some patients metastasis is found not in the hottest sentinel node but in that with only faint radioactivity and the use of higher doses may be recommended to detect faint radioactivity of positive nodes.

Exposure to unnecessary irradiation should be avoided whenever possible and further study of the optimal dose is awaited.

T. Watanabe
Department of Surgery 2
Fukushima Medical University
1 Hikarigaoka
Fukushima 960–1295
Japan

1 van der Ent FW, Kengen RA, van der Pol HA, Povel JA, Stroeken HJ, Hoofwijk AG. Halsted revisited: internal mammary sentinel lymph node biopsy in breast cancer. *Ann Surg* 2001; **234:** 79–84.
2 Valdes-Olmos RA, Jansen L, Hoefnagel CA, Nieweg OE, Muller SH, Rutgers EJ *et al.* Evaluation of mammary lymphoscintigraphy by a single intratumoral injection for sentinel node identification. *J Nucl Med* 2000; **41:** 1500–6.
3 Nissan A, Spira RM, Chisin R, Zamir O, Prus D, Klein M *et al.* Sentinel lymph node biopsy in breast cancer: a validation study and preliminary results. *Harefuah* 2001; **140:** 468–70, 567.

A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men (*Br J Surg* 2001; 88: 941–4)

Sir

This paper provides a convincing argument in support of a single scan at age 65 years but the number of patients involved is relatively small. Although a single scan would substantially reduce the costs involved, an earlier and larger study showed that rescreening in subjects only with infrarenal aortic diameters of 2·5 cm or greater on the initial ultrasonography scan would have missed more than two-thirds of new abdominal aortic aneurysms (AAAs)[1].

It will become necessary to calculate the cost:benefi ratio of such a screening programme. The mortality and morbidity rates of treatment for AAA are significantly higher than for breast or colonic carcinoma, for example and the disease itself is not universally fatal. The high prevalence of cardiovascular disease in patients with AAA and competing causes of morbidity and mortality may diminish the benefit of detecting asymptomatic aneurysm particularly in older populations. Aneurysms requiring treatment occur uncommonly and it may be that targeting subsets of the population could improve cost effectiveness. For example, there is little point screening a patient who is unfit for a general anaesthetic or whose other medical problems overshadow the need for intervention.

S. Mehta
I. A. A. Hindmarsh
Department of Surgery
Broomfield Hospital
Broomfield
Chelmsford CM1 7ET
UK

1 Lederle FA, Johnson GR, Wilson SE, Littooy FN, Krupski WC, Bandyk D *et al.* Yield of repeated screening for abdominal aortic aneurysm after a 4-year interval. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000; **160**: 1117–21.

Author's reply

Sir

Contrasting somewhat to our study, Dr Lederle's group has demonstrated a small but definite incidence of new aneurysm formation 4 years after normal initial ultrasonographic screening and concludes, nevertheless, that rescreening after a 4-year interval is not worthwhile[1].

I believe that the differences between the two studies are more apparent than real and can largely be explained by the different ages of the subjects screened and by a different definition of aneurysm.

The study by Lederle *et al.* included patients as young as age 50 years and used a threshold of 3·0 cm diameter to define an abnormal aorta, whereas all screening in Gloucestershire was performed at age 65 years and used a threshold of 2·6 cm diameter. Without the raw data from their study it is difficult to be certain, but I suspect that the application of a 2·6-cm threshold to subjects of 65 years or older would have yielded very similar results – that no clinically significant aneurysms developed during follow-up.

We remain confident that the combination of screening at age 65 years with follow-up of patients with aortas of 2·6 cm diameter or greater offers a very practical approach to effective aneurysm screening with a single examination.

However, up to 10 per cent of ruptured aneurysms occur before the age of 65 years. Screening to identify these patients would need to be carried out at the age of 55 or 60 years and would almost certainly necessitate the cost of a second scan 5 or 10 years later.

B. P. Heather
Gloucester Vascular Group
Gloucestershire Royal Hospital
Great Western Road
Gloucester GL1 3NN
UK

1 Lederle FA, Johnson GR, Wilson SE, Littooy FN, Krupski WC, Bandyk D *et al.* Yield of repeated screening for abdominal aortic aneurysm after a 4-year interval. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000; **160**: 1117–21.

Perioperative Medicine

A. Nicholls and I. Wilson (eds)

185 × 105 mm. Pp. 384. Illustrated. 2000. Oxford: Oxford University Press. £19·95.

This book deals with the medical care of the surgical patient and is aimed at junior surgeons and anaesthetists. It is divided into four sections: general medical issues on surgical wards, preoperative care of patients with chronic medical disorders, postoperative complications and sensible prescribing. The book is easy to read with the major headings and pages listed at the beginning of each chapter, the use of bullet points and numerous clearly presented tables. Some chapters would have benefited from the use of flow diagrams and increased cross-referencing between related chapters and issues. There are a few areas of controversy regarding resuscitation decisions and preoptimization of high-risk patients and there are one or two surprising omissions in the cardiac sections, such as the value of troponin measurements.

Overall it is a fairly comprehensive book and the guidelines represent safe, pragmatic and acceptable practice. The sections on informed consent, teamwork, fluid management, treatment of postoperative pain and nausea, how and which antibiotics to prescribe and the use of physiotherapy deserve specific mention. Issues of assessment of chronic and acute medical conditions are well covered, along with first-line management, reassessment and advice on when to refer to a specialist or ask for more senior help. Junior surgical staff will find this practical handbook a valuable source of reference and advice.

J. Brittenden
Ward 36
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZG
UK

Transplantation Surgery

N. S. Hakim and G. M. Danovitch (eds)

275 × 200 mm. Pp. 450. Illustrated. 2001. London: Springer. £80·00.

This book is based on the experience of many distinguished authors working in the field of transplantation medicine and surgery. It contains 21 chapters that provide detailed information on various aspects of transplantation, including new technologies such as laparoscopic nephrectomy, non-heart-beating kidney donation and living-related liver transplantation. In addition important issues in transplantation immunology, organ preservation and immunosuppression are highlighted. This book, therefore, contains a broad coverage of aspects related to transplantation. Each chapter begins with an outline of the aims and finishes with a number of questions. In this way the authors succeed in focusing attention on the most important sections. The chapters are well referenced. All in all this is an excellent book that deserves recognition and widespread use.

J. N. M. IJzermans
Department of Surgery
Dijkzigt Hospital
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands

Operating within the Law

B. Campbell, K. Callum and N. A. Peacock

210 × 149 mm. Pp. 254. 2001. Shifnal: TFM Publishing. £24·95.

This guide appears at a time when there is an ever-increasing probability of surgeons encountering litigation. Much of its appeal is that it is more comprehensive than a pocketbook and less daunting than an exhaustive tome. It is didactic, clear and well laid out. The text follows a logical sequence and includes a list of references and suggestions for further reading at the end of each chapter. I found the appendices (e.g. 'Draft structure of a medical report') particularly useful. The authors make extensive use of actual cases to clarify what otherwise might seem perplexing problems and confusing issues. Surgeons may 'smile smugly' (page 35) to read that even lawyers can be 'sent into a spin' (page 39) by the intricacies of surgical litigation.

This book is eminently readable and is in every way a practical guide to the subject.

S. Homer-Vanniasinkam
Vascular Surgical Unit
The General Infirmary at Leeds
Great George Street
Leeds LS1 3EX
UK

Facial Rejuvenation

P. J. Carniol (ed.)

260 × 182 mm. Pp. 446. Illustrated. 2000. Chichester: Wiley-Liss. £139·00.

In his preface, the editor, Paul Carniol, points the reader towards 'a multitude of new techniques and technology that have altered and improved our ability to rejuvenate our patients'. He has brought together authors with extensive experience of various procedures in an attempt to highlight the advances and variations in technology. This book however, suffers from the disadvantage of many multi-author texts in that it is difficult to read because of the variations in style; there is no uniformity in either presentation or content from chapter to chapter. The use of line diagrams, photographs, tables and referencing are variable. The volume does, however, highlight the difficulties in obtaining comparable preoperative and postoperative photographs. The use of jewellery and cosmetics, and variations in exposure and lighting, are all well known methods of altering facial appearance and are illustrated in several chapters.

This book has brought together a variety of new techniques used in facial rejuvenation, described by obvious enthusiasts of their subject. It is by composition selective and is not a comprehensive text, and it is difficult to identify its primary aim or target audience. Half the chapters (13–24) concern laser techniques that are adequately and more comprehensively covered in texts that are already available. A single chapter on skeletal surgery can serve only as an introduction to this topic which, again, is covered in several maxillofacial texts. The techniques for face-lifting and neck-lifting are individual methods that give no indication of what other variations are available.

One of the keys to successful facial surgery is the identification of the high-risk patient, which is associated with both the physical and mental condition of the patient. Disappointingly, in this book there is little emphasis on preoperative assessment, particularly physiological and psychological assessment, preoperative counselling, and the identification of the patient with unrealistic expectations. Similarly, complications are, on the whole, very poorly dealt with, perhaps again because there is no chapter about patient counselling or how to deal with the dissatisfied patient. The overall impression of this volume is of a random selection of interesting techniques, written by enthusiasts who tend to dwell on positive aspects rather than problems, complications or limitations of their art. This is not a book for the novice or young trainee because it does not cover the subjects in sufficient detail. Although facial rejuvenation is topical, I feel this book will have only a limited appeal.

D. Soutar
Canniesburn Hospital
Bearsden
Glasgow G61 1QL
UK

Scientific Surgery

Taft C, Karlsson J, Gelin J, Jivegard L, Sandstrom R, Arfvidsson B *et al.* Treatment efficacy of intermittent claudication by invasive therapy, supervised physical exercise training compared to no treatment in unselected randomized patients II: 1 year results of health-related quality of life. *Eur J Vasc Endovasc Surg* 2001; **22:** 114–23.

A total of 253 patients were randomized into one of three groups. After 1 year invasive therapy was most effective at alleviating illness-specific symptoms; however, treatment effects were moderate and the level of evidence supporting invasive therapy was modest.

Cole BF, Gelber RD, Gelber S, Coates AS, Goldhirsch A. Polychemotherapy for early breast cancer: an overview of the randomised clinical trials with quality-adjusted survival analysis. *Lancet* 2001; **358:** 277–86.

This analysis concerned 18 000 women treated in randomized trials with at least 10 years of follow-up. Quality-adjusted survival was improved, particularly in women under 50 years old, and to a lesser extent in women aged between 50 and 70 years.

Horvath OP, Kalmar K, Cseke L, Poto L, Zambo K. Nutritional and life-quality consequences of aboral pouch construction after total gastrectomy: a randomized, controlled study. *Eur J Surg Oncol* 2001; **27:** 558–63.

Some 46 patients who had total gastrectomy for malignancy were included. Reconstruction with a pouch did not affect body-weight, but significantly improved lipid absorption and quality of life at 24 months.

Post S, Kraus T, Muller-Reinartz U, Weiss C, Kortmann H, Quentmeier A *et al.* Dacron *versus* polytetrafluoroethylene grafts for femoropopliteal bypass: a prospective randomised multicentre trial. *Eur J Vasc Endovasc Surg* 2001; **22:** 226–31.

There were 194 patients in the final analysis. At median follow-up of 36 months, there was no difference in primary patency rates: Dacron 64 per cent *versus* polytetrafluoroethylene 61 per cent. A distal anastomosis below the knee was the main predictor of graft failure.

Takayama T, Makuuchi M, Kubota K, Harihara Y, Hui AM, Sano K *et al.* Randomized comparison of ultrasonic *versus* clamp transection of the liver. *Arch Surg* 2001; **136:** 922–8.

In a trial including 132 patients, ultrasonic dissection did not reduce median blood loss (515 *versus* 452 ml), transection time or transection speed. The clamp crushing method improved the quality of the hepatectomy and (non-significantly) reduced postoperative morbidity.

Pacelli F, Bossola M, Papa V, Malerba M, Modesti C, Sgadari A *et al.* Enteral *versus* parenteral nutrition after major abdominal surgery: an even match. *Arch Surg* 2001; **136:** 933–6.

Some 241 patients were included. There were no significant differences in the rates of postoperative morbidity (enteral 38 per cent *versus* parenteral 39 per cent) or mortality (6 *versus* 2·5 per cent respectively).

Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M *et al.* Three months *versus* 1 year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001; **345:** 165–9.

The study included 267 patients followed for a mean of 3 years. The additional 9 months of warfarin therapy reduced the rate of recurrent deep venous thrombosis in the first year from 8 to 1 per cent ($P = 0.003$), but thereafter the rate was similar in both groups (5 per cent per year).

Janicke F, Prechtl A, Thomssen C, Harbeck N, Meisner C, Untch M *et al.* Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type I. *J Natl Cancer Inst* 2001; **93:** 913–20.

Some 241 women with low cancer tissue plasminogen activator levels were observed, 315 with raised levels were randomly allocated chemotherapy. After 3 years, the relative risk of breast cancer recurrence was reduced to 0·56 (95 per cent confidence interval 0·25–1·28) by chemotherapy.

Naumann M, Lowe NJ on behalf of the Hyperhidrosis Clinical Study Group. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomized, parallel group, double blind, placebo controlled trial. *BMJ* 2001; **323:** 596–9.

A total of 307 patients were compared. Botulinum toxin reduced sweating at 4 weeks in 94 per cent of treated patients, compared with 36 per cent in the placebo group. The respective values at 16 weeks were 82 and 21 per cent.

Watson DI, Jamieson GG, Devitt PG, Kennedy JA, Ellis T, Ackroyd R *et al.* A prospective randomized trial of laparoscopic Nissen fundoplication with anterior *versus* posterior hiatal repair. *Arch Surg* 2001; **136:** 745–51.

There was no significant difference in symptom relief or patient satisfaction in this trial including 102 patients. Six patients who had posterior repair needed reoperation.

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Instructions to authors

BJS publishes original articles, reviews and leading articles all of which are submitted to peer review.

An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject. It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap. Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Send four copies of original articles and other editorial matter to: The Editor, *BJS*, Blackwell Science Ltd, 25 John Street, London WC1N 2BS, UK. Telephone: 0207 404 1831; facsimile: 0207 404 1927. A version on disk must accompany all submitted material. For instructions on how to do this, see below. Books for review should be sent to the same address

A covering letter must accompany all submissions, must be signed by all authors and must state whether an abstract of the work has been published - please provide an appropriate reference. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The Journal takes very seriously its obligation to assess and declare any actual or potential conflicts of interest. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support. The first named author is responsible for ensuring that all authors have seen, approved and are fully conversant with its contents The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; 308 39–42) and the COPE guidelines on good publication practice (www. publicationethics.org.uk). If a paper has more than six authors you must justify the inclusion of all names. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995, 345· 668) The Editors are of the view that those with a peripheral association with the work should simply be acknowledged (*BJS* 2000; 87: 1284–6).

Disks

IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors. Proofs will be sent via e-mail as an Acrobat portable document format (PDF) file.

Rejected manuscripts and illustrations will not normally be returned.

Ethics

Material relating to human investigation and animal experiments must comply with and be approved by local ethics committees It must conform to standards currently applied in the country of origin. The Journal reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication of any details or photographs that might identify an individual. Submit evidence of such consent with the manuscript.

Preparation of manuscripts

BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; 336: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2 95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

Reviews and meta-analyses of randomized trials

The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; 354: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK

Leading articles

The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal Responses can be sent

electronically via the *BJS* website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (www.consort-statement.org).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the P value. Actual P values should be reported to three decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

Index to Volume 88

Author index

Abbott, C. R., 951
Abdalla, E. K., 165
Åberg, C., 273
Abidia, A. F., 1590
Acosta, S., 385
Adachi, Y., 873
Adam, D. J., 1196
Adawi, D., 228
Agarwal, G., 708
Ågren, M. S., 228
Ahlman, H., 865
Aikou, T., 988
Airey, M., 529
Aishima, S., 1463
Akaike, M., 1596
Akhavani, M. A., 1363
Akiba, S., 988
Alhava, E., 1006
Al-Khairy, G., 1157
Allcock, P. A., 683
Allen-Mersh, T. G., 1307
Allgar, V., 878
Altomare, D. F., 669, 1481, 1487
A-Malik, R., 146
Anand, P., 545
Ananthakrishnan, N., 1054
Anderson, J. H., 1392
Andersson, M., 273
Andersson, R. E. B., 1387
Ando, M., 1084
Andreu, J., 1321
Anthony, A. A., 629
Anup, R., 393
Appelros, S., 216
Armstrong, A. M., 235
Armstrong, G. R. A., 1357
Arnold, J. A. C., 389
Arroyo, A., 1321
Arulampalam, T. H. A., 176
Asao, T., 128
Aspinall, R., 298
Atken, W. S., 107
Attwood, S. E. A., 1357
Austen Jr, W. G., 825
Ayabe, H., 831
Ayhan Krizu, M., 464
Ayub, K., 1189

Baako, B. N., 1595
Badosa, F., 1366
Badrinath, S., 1054
Bais, J. E., 569
Baker, J. L., 382
Balasubramanian, K. A., 393
Baldwin, the late P. J., 1525
Balladur, P., 627
Ballantyne, A., 720
Banks, R. E., 878
Barclay, G. R., 878
Barraclough, B., 1234
Barrett, D. A., 1613
Bartram, C. I., 853
Bartsch, D. K., 1403
Basse, L., 1498
Bassi, C., 376
Bates, T., 1283
Bauer, M., 450
Baulieux, J., 1456
Bauwens, K., 901
Bayly, P. J. M., 687
Beattie, G. C., 850
Beckman-Suurkula, M., 865
Bedi, R., 206
Beelen, R. H. J., 539
Beets-Tan, R. G. H., 1506
Belcher, G., 1376
Belghiti, J., 73
Bemelman, W. A , 693, 1492
Benhamiche, A. M., 1221
Bergenfelz, A., 1403
Bergh, C. H., 865
Bergkvist, L., 1644
Besnard, A. P. E., 123
Bhat, M. A., 536
Biffin, A., 278
Bijnen, A. B., 251
Birks, M., 553
Bjorck, M., 385
Bjórquist, P., 286
Blanshard, K. S., 77
Bleeker, W. A., 101
Blumgart, L. H., 808
Bokey, E. L., 1476
Bomfim, V., 1209
Bonthuis, F., 1258
Booth, M. I., 577
Borgstrom, A., 216
Bose, M., 1425
Bosma, A., 48
Bothin, C., 143
Boucher, N. R., 290
Bouchier-Hayes, D. J., 1105
Boulos, P. B., 1037
Bouter, L. M., 1285
Boyages, J., 860, 1513
Boyle, J. R., 958
Bozer, M., 85
Bradbury, A. W., 82, 1196
Bradshaw, H. D., 290
Braithwaite, B. D., 1427
Brand, A., 267
Breeman, W. A. P., 31
Bromwich, E., 1178
Brongers, E. P., 1382
Brooks, M. D., 389
Brouwer, K. J., 1578
Brown, G., 1628
Bruce, J., 1122, 1157
Brunt, L. M., 481
Bryce, R., 662
Büchler, M. W., 90, 975, 1501
Buchmuller, A., 913
Buikema, H., 1201
Bundred, N. J., 412
Buntzen, S., 1637
Burke, D , 241
Busch, O. R. C., 1467
Buth, J., 1059
Butt, A. K., 206
Byrne, J. P., 1357

Caidahl, K., 865
Calpena, R., 1321
Camilleri-Brennan, J., 1617
Candela, F., 1321
Canuti, S., 669
Carroll, T. A., 724
Cassar, K., 1341
Cedermark, B., 839
Celebioglu, F., 1644
Celik, I., 1403
Chalmers, R. T. A., 82
Chambers, A. J., 294
Chambers, M. G., 1029
Chambers, W., 1602
Chambers, W. A., 1122
Chan, K. C., 412
Chant, H., 77
Chapuis, P. H., 1476
Charbon, J. A., 1059
Charitou, A. N., 837
Charles, J., 278
Charnsangavej, C., 325
Charny, C. K., 808
Cheah, W. K., 45
Chell, S., 529
Chen, H.-H., 1513
Cheong, W. K., 357
Chetter, I. C., 1590
Cheynel, N., 1221
Chipponi, J., 1456
Choe, K J , 1408
Christensen, M., 1228
Christensen, P., 1637
Chu, K. W., 1607
Chua, B., 1513
Chui, A. K. K., 681
Chuman, Y., 988
Clarke, P. A., 564
Collin, J., 814, 1281
Connelly, J., 529
Connolly, E. M., 41
Cordner, S. M., 1099
Corless, D. J., 298
Coskun, A., 85
Costa, D. C., 176
Crellin, A. M., 338
Crombie, N., 1324
Crotty, T. B., 945
Crow, P., 941
Crumplin, M. K. H., 278
Cuesta, M. A., 539
Cullum, N. A., 4
Cuypers, P. W. M., 1059

Damm, S., 1644
Dammers, R., 816
Darmon, J.-Y., 913
Dashwood, M. R., 1209
David, E., 1194
Davidson, N., 662
Davies, J. N., 77
Davis, P. A., 298
de Beaux, A. C., 1117
de Boer, R., 118
de Boer, W. J., 433
de Bree, E., 458
de Cossart, L., 323
De Fazio, M., 1487
de Jong, M., 31
de Man, R. A., 207
de Manzoni, G., 419
de Ruiter, P., 251
de Vet, H. C. W., 1285
de Vries, J. D. H., 305
de Wilt, J. H. W., 207
de Wit, L. T., 1467
Deasy, J., 41
Decousus, H., 913
Dehn, T. C. B., 577
Delaney, C. P., 1533
Delis, K. T., 523
Dematteo, R. P., 808
Dent, O. F., 1476
Desoky, A., 1049
Di Leo, A., 419
Dirsch, O., 90
Dobson, P. M., 687
Dodi, G., 1481
Dolenko, B., 1234
Dowidar, N., 588
Dresner, S. M., 1346
Duell, R. M., 773

Duff, M., 114
Duncan, J. L., 1341
Duzgun, S. A., 85
Dzik-Jurasz, A. S. K., 1628

Earnshaw, J. J., 941, 1344
Eccles, S. A., 1628
Edwards, D. P., 360
Edwards, P. R., 1178
Egger, B., 90
Ejstrud, P., 1001
Ekkernkamp, A., 901
El-Assal, O. N., 515
Ell, P. J., 176
Elliott, T. B., 1183
Ellis, I. O., 1324
Ellul, J. P. M., 1249
Elston, C. W., 1324
Erceg, J., 371
Ergun, H., 464
Erlandsen, E. J., 1472
Ettorre, G. M., 73
Eu, K.-W., 357, 801, 1449
Evans, D. B., 325
Evans, J. D., 1245
Evans, S. M., 82

Fabregat, J., 980
Facer, P., 545
Faivre, J., 1221
Falconi, M., 376
Falk, K., 286
Falk, P., 148
Farges, O., 73
Farouk, R., 553
Farrell, T. M., 1649
Farthing, M. J. G., 1425
Fasting, H., 1066
Favuzza, J., 825
Fazio, V. W., 1533, 1623
Fearon, K. C. H, 255, 588
Fernando, K. J., 309
Fide, C. J., 1216
Figueras, J., 980
Filbey, D., 1209
Filtenborg Tvedskov, T., 1413
Finch, J. G., 629
Finlay, I. G., 1392
Fleming, W. R., 1183
Fong, Y., 808
Fosh, B. G., 629
Foster, M. E., 278
Foulkes, R., 235
Foy, C., 1216, 1344
Franchello, A., 1194
Franklin, I. J., 935
Frisell, J., 1644
Frommeyer, H. S., 808
Fujii, H., 1110
Fukao, K., 364

Gabrielli, F., 669
Gandhi, A., 412
Ganio, E., 669
Gannon, C., 235
García, P., 1321
Gardien, M., 1059
Gardiner, E. D., 1590
Gardiner, K. R., 235
Garvie, N., 405
Gastinger, I., 1397
Gayet, B., 1456
Geelkerken, R. H., 693
Geh, J. I., 338
Gelpí, E., 1366
George, M. L., 1628
Gerhards, M. F., 48
Gerritsen, A. A. M., 1285
Gillett, D., 1234
Gillett, G., 897
Gillick, J., 1539
Gloor, B., 975
Gluch, L., 1234
Glynne-Jones, R., 338
Godden, D. J., 1341
Goh, P. M. Y., 45
Gooszen, A. W., 693
Gooszen, H. G., 569, 693
Gotoda, T., 444
Gough, M. J., 951
Gouillat, C., 1456
Gouma, D. J., 48, 251, 1467
Grab, D., 698
Gray, D. W. R., 1330
Green, M. H. A., 773
Griffin, S. M., 1346
Griffioen, G., 1492
Grogan, M., 1513
Guevara, O., 73
Guillou, P. J., 1352
Gupta, A., 1296
Gupta, S. K., 708
Gurhan, I., 464
Guthrie, J. A., 1352
Gutt, C. N., 371

Haapiainen, R., 222
Haga, N., 128
Haggart, P. C., 1196
Halligan, S., 853
Halverson, A. L., 1533
Hamming, J. F., 884
Han-Geurts, I. J. M., 1578
Hardy, K. J., 1183
Harmey, J. H., 1105
Harris, G. J. C., 1623
Hart, A. A. M., 123
Hartley, P., 52
Hase, K., 994
Hatakeyama, K., 675
Haverlag, R., 1258
Hawkins, K., 433
Hayes, N., 1346
Hayne, D., 1037
Heah, S. M., 357
Heald, R. J., 360
Heather, B. P., 941, 1344
Heaton, N. D., 70
Hechtman, H. B., 825
Henneberg, E. W., 1066, 1472
Henwood, M., 564
Herbst, F., 241
Hermans, J., 101, 267
Hicks, M. E., 165
Hill, A. D. K., 114
Hillen, H. F. P., 118
Himmelreich, U., 1234
Hirohashi, K., 969
Hiroshige, S., 59
Ho, Y.-H., 1449
Hoekstra, H. J., 433
Holloway, B., 588
Holm, T., 839
Holmdahl, L., 148, 286
Homer-Vanniasinkam, S., 951, 1169, 1335
Höög, A., 557
Hop, W. C. J., 1059
Hornung, H. M., 1092
Horrocks, M., 1376
Hosie, K. B., 1363
Hosouchi, Y., 128
Hotter, G., 1366
Houbiers, J. G. A., 267
Huang, Y., 90
Hulscher, J. B. F., 715
Hunt, D. R., 486
Hunter, J. G., 1649

Iizuka, H., 1110
IJzermans, J. N. M., 207
Ikegami, T., 59
Imamura, M., 426
Inglin, R., 90
Inomata, M., 873
Irving, M., 190
Ishizawa, T., 988
Ivarsson, M.-L., 148

Jager, G. J., 844
Jain, A. S., 683
Jakubowski, J., 724
James, M. J., 290
Jamieson, G. G., 1117
Jamieson, N. V., 773
Jansen, L., 305
Jarnagin, W. R., 808
Jaurrieta, E., 980
Jawaheer, G., 720
Jeekel, J., 1258, 1578
Jeng, K.-S., 986
Jennings, G., 235
Jeppsson, B., 228
Johansson, H., 273, 839
Johnson, B. F., 1590
Johnson, C. D., 216, 662, 773
Johnson, J. N., 1025
Jonas, M., 1613
Jones, J. W., 1153
Jones, P. F., 1570
Jones, R. McL., 1183
Jones, W. O., 137
Joosten, J., 844
Juul, S., 1228

Kaag, M. M., 458
Kaas, R., 123
Kamiya, J., 1084
Kamm, M. A., 853, 1029
Kar, D. K., 708
Katai, H., 444
Katballe, N., 1228
Kate, V., 1054
Kato, H., 439
Kawamoto, T., 364
Kearns, S. R., 41
Keaveny, T. V., 945
Kehlet, H , 1498
Kelman, J., 82
Kemppainen, E., 222, 679
Kerwat, R., 278
Khan, A. A., 206
Kim, J.-P., 1408
Kim, W. H., 1408
Kim, Z. G., 371
Kimijima, I., 704
King, P. M., 1122
Kinoshita, H., 969
Kirk, S. J., 235
Kirwan, W. O., 246
Kitano, S., 873
Kite, P., 878
Kjellman, P., 557
Klauss, W., 698
Klein Kranenbarg, W. M., 267
Kmiot, W. A., 853
Knight, J. S., 553
Knowles, C. H., 405, 545
Knox, W. F., 412
Koch, A., 1397
Kocher, H. M., 1249
Kohno, H., 515
Koike, N., 364
Kokawa, A., 439
Kokki, H., 510
Koksoy, C., 464
Kono, K., 1110
Kootstra, G., 500
Kopp, I., 1403
Koretz, K., 698
Koukourou, A., 931
Krabbe, P. F. M., 643
Kreienberg, R., 698
Krenning, E. P., 31
Krikke, A., 1382
Krogh, K., 1637
Kroon, B. B. R., 305

Krukowski, Z. H., 1122, 1157
Kubo, S., 969
Kuehn, T., 698
Kuhan, G., 1590
Kuijt, G. P., 1639
Kum, C. K., 45
Kurvers, H. A. J. M., 816
Kuwano, H., 128
Kuzu, L, 464
Kylanpää-Back, M.-L., 222
Kyriakides, C., 825

La Torre, F., 1481
Lai, P. B. S., 133, 681
Lalloo, S., 1073
Lamb, P. J., 1346
Lambert, A. W., 1363
Lång, M., 1006
Langenhoff, B. S., 643
Langer, P., 1403
Laporte, S., 913
Larsen, J. F., 1001
Larsson, C., 557
Lau, J. W. Y., 133
Lau, W. Y., 681
Launois, B., 1442
Laurberg, S., 200, 1228, 1637
Lau-Werner, U., 1092
Lavery, I. C., 1623
Law, W. L., 1607
Lean, C., 1234
Learoyd, D. L., 557
Lee, F. Y. J., 133
Lee, H. K., 1408
Lee, J. E., 325
Lee, K. U., 1408
Lennox, A. F., 523
Lenzi, J. E., 45
Leppington-Clarke, A., 360
Leung, K. F., 681
Leung, K. L., 133, 681
Li, Z., 426
Libertiny, G., 1330
Liem, I. H., 1639
Liew, C. T., 681
Li-Ling, J., 190
Liljegren, G., 1644
Lin, M.-C., 210
Lindholt, J. S., 625, 1066, 1472
Linklater, K., 1249
Lintula, H., 510
Lippert, H., 1397
Little, J. M., 769
Liu, T.-J., 210
Loizidou, M., 176
Lone, G. N., 536
Lord, R. S. A., 294
Lorenz, M., 371
Loudon, M. A., 850
Lucarotti, M. E., 1216
Ludman, P. F., 1196
Lunde, O. C., 400
Lunniss, P. J., 405
Lupo, F., 1194
Lyon, W., 931

Machin, D., 801
MacMahon, A. J., 255
Maddern, G. J., 629, 1442
Madsen, J. L., 1498
Maeda, M., 426
Majid, M., 4
Mall, J. W., 99
Malouf, A. J., 1029
Malycha, P., 1234
Manfredi, S., 1221
Manson, J. McK., 1077
Marijnen, C. A. M., 1556
Marquet, R. L., 31, 1258
Martignoni, M. E., 975
Martino, P., 1487
Marusch, F., 1397
Masclee, A. A. M., 569, 1492, 1519
Mathie, R. T., 1189
Matsumoto, Y., 1110
Matthews, J. N. S., 687
Maughan, P. J., 899
Maurer, C. A., 1501
Mavor, A. I. D., 951, 1169
Mayer, J., 679
McCarthy, P., 945
McCollum, P. T., 1590
McCourtney, J. S., 1602
McCullough, L. B., 1153
McDermott, E. W., 114
McDermott, F. T., 1099
McDonnell, C. O., 1105
McEwen, J., 1155
McGreal, G., 114
McGuinness, C. L., 389
McKee, R. F., 1392
McNally, S., 41
McNamara, D. A., 41
Mearadji, A., 31
Medical Research Council Laparoscopic Groin Hernia Trial Group, 653
Meeuwis, J. D., 884
Mehigan, D., 945
Meijer, S., 539
Meijerink, W. J. H. J., 1492
Melega, E., 1481
Mels, A. K., 539
Memeo, V., 1487
Menger, M. D., 450
Meny, B., 1221
Mercer, S. J., 1363
Messina, M., 557
Metcalfe, M., 261
Michaels, J. A., 964
Midtvedt, T., 143
Miettinen, P., 1006
Mikhailidis, D. P., 787
Milito, G., 669
Mishra, S. K., 708
Mismetti, P., 913
Mithal, A., 708
Mochiki, E., 128
Mochizuki, H., 994
Modaresi, K. B., 389
Modhwadia, D., 853
Mofidi, R., 945
Mohan Singh, M. P., 536
Moodley, J., 1073
Moore Jr, F. D., 825
Moore, P. S., 419
Moran, B. J., 360
Morren, G. L., 1506
Morris, C. D., 1357
Morris, P. J., 1330
Mortensen, N. J. McC., 1558
Moses, A. G. W., 588
Mountford, C. E., 1234
Muiesan, P., 70
Mulder, N. H., 101
Müller, C., 1092
Müller, C. A., 975
Muller, J. M., 99
Muller, M. J., 583
Munro, F. D., 720
Murie, J. A., 82, 1281
Murphy, G. J., 261
Mutze, S., 901

Nagakura, S., 675
Nagasue, N., 515
Nagino, M., 1084
Nakabayashi, T., 128
Nakagoe, T., 831
Nakanishi, Y., 439
Neary, B., 1344
Neelakandhan, K. S., 536
Neoptolemos, J. P., 679
Nesbakken, A., 400
Netzer, P., 1501
New, N. E., 837
Newell, M., 405
Newland, R. C., 1476
Ng, A. K. T., 137
Nicholls, R. J., 241, 853, 1602
Nicholls, T., 853
Nicholson, M. L., 261, 484, 1429
Nicolaides, A. N., 523
Nieweg, O. E., 305
Nikulin, A. E., 1234
Nilsson, T. K., 385
Nimura, Y., 1084
Nishizaki, T., 59
Niskanen, M., 1006
Niwa, K., 988
Noguchi, Y., 1596
Nygaard, K., 400

Ó Súilleabháin, C. B., 1392
O'Boyle, C., 1117
O'Dwyer, S. T., 107
O'Higgins, N. J., 114
O'Leary, D. P., 1216
O'Meara, S. M., 4
O'Reilly, G., 724
O'Riordain, D. S., 163, 1352
O'Sullivan, G. C., 161
Obertop, H., 715, 1467
Offerhaus, G. J. A., 715
Ohta, R., 59
Ohtake, T., 704
Okada, M., 143
Olsson, L., 273
Ono, H., 444
Ono, T., 515
Oostvogel, H. J. M., 884
Ørntoft, T. F., 1228
Østergaard, L., 1066
Otter, R., 101
Oude Egbrink, M. G. A., 816
Ozardalı, I., 85

P'eng, F.-K., 210
Padayachee, T. S., 389
Padhani, A. R., 1628
Painter, J. E., 107
Paisley, A. M., 1525
Palfreyman, S., 964
Papadatos, G., 860
Papp, L., 82
Parc, R., 627
Park, K. G. M., 1157
Parker, S. J., 22
Partensky, C., 1456
Pasieka, J. L., 321
Patel, H., 1307
Patel, S., 1249
Paterson-Brown, S., 1525
Pedersen, A. G., 200
Pedersen, V., 1001
Pederzoli, P., 376
Peels, C. H., 1059
Pegg, S. P., 583
Perbeck, L., 143
Pérez, F., 1321
Pershad, S., 1073
Peston, D., 935
Peterse, J. L., 123
Petersen, O. B., 200
Petersson, U., 216
Petruckevitch, A., 52
Pettigrew, G. J., 837
Pi, F., 1366
Pinder, S. E., 1324
Pisters, P. W. T., 325
Plukker, J. T. M., 101, 1382
Pollmann, C., 99
Poobalan, A. S., 1122
Porzsolt, F., 901
Poskitt, K. R., 941

Potten, C. S., 107, 412
Powell, J. T., 935
Powrie, F., 1558
Prats, N., 1366
Price, M. L., 687
Pross, M., 1397
Prytherch, D. R., 958
Psarianos, T., 860
Puntis, M., 662
Puolakkainen, P., 222, 679
Puri, P., 1539
Pye, J. K., 278

Qvist, N., 200

Rademacher, G., 901
Rafecas, A., 980
Rahr, H. B., 1001
Ramos, E., 980
Rampaul, R. S., 1324
Ramsay, G., 816
Rangan, A. M., 860
Raraty, M., 679
Rasmussen, M. S., 1413
Rastad, J., 708
Rat, P., 1221
Rathore, R. S., 536
Rauws, E. A. J., 48
Redke, F., 1001
Redmond, H. P., 246
Reeves, B., 52
Rela, M., 70
Remzi, F. H., 1533
Renehan, A. G., 107
Renwick, P. M., 1590
Renzulli, P., 1501
Repo, H., 222
Rice, J., 931
Richardson, D. L., 1346
Richardson, W. S., 1649
Ride, E., 1352
Riemer, V., 371
Rigby, K. A., 964
Rinaldi, M., 1481
Rinaldi, M., 1487
Ringers, J., 1519
Rizzetto, M., 1194
Robbs, J. V., 1073
Roberts, S. A., 1077
Robertson, J. F. R., 1324
Robinson, B., 1533
Robinson, B. G., 557
Robless, P., 787
Rodiger, O., 99
Roesken, F., 450
Rolles, K., 52
Romano, G., 1481
Rønning, H., 200
Roozendaal, G. K., 305
Rosario, D. J., 290
Roselló Catafau, J., 1366
Ross, J. A., 588

Rottier, K., 433
Roumen, R. M. H., 118, 1639
Rowlands, T. E., 1335
Rücker, M., 450
Ruers, T. J. M., 643, 844
Rule, M. R., 583
Rumley, A., 878
Russell, E. M., 1157
Russell, P., 1234
Rutgers, E. J. T., 123
Rutqvist, L. E., 839
Rutten, H. J. T., 118

Saeb-Parsey, K., 1363
Salizzoni, M., 1194
Sallustio, P. L., 1487
Salvia, R., 376
Sanders, G., 1363
Sano, T., 444, 1084
Santjohanser, C., 698
Sarela, A., 163
Sarela, A. I., 1352
Saric, J., 1456
Sasako, M., 444
Sato, F., 426
Sato, K., 873
Sauvanet, A., 73
Sawai, T., 831
Scarpa, A., 419
Schafer, T., 450
Scheper, R. J., 539
Schildberg, F. W., 1092
Schilling, M. K., 1501
Schmidt, U., 1397
Scholefield, J. H., 1613
Scholten, R. J. P. M., 1285
Schraffordt Koops, H., 305
Schurink, G. W. H., 500
Schwartz, L. H., 808
Schwenk, W., 99
Scott, D. J. A., 1583
Scott, M. H., 1245
Scott, N. A., 146
Scott, S. M., 405
Sehouli, J., 901
Sekikawa, T., 1110
Senagore, A. J., 1533
Seow-Choen, F., 1, 357, 801, 1449
Serracino-Inglott, F., 1189
Sexton, R., 360
Seymour, M. T., 1352
Shalaby, R., 1049
Shalet, S. M., 107
Shaw, E., 941
Shaw, J. H. F., 137
Shaw, P. N., 1613
Sheehan, S. J., 945
Sheen, I.-S., 986
Sheldon, T. A., 4
Shimada, M., 1463
Shimada, Y., 426

Shimoda, T., 444
Shirabe, K., 1463
Shirai, Y., 675
Shiraishi, N., 873
Shishido, F., 704
Shoda, J., 364
Singh, B., 1073, 1558
Siriwardena, A. K., 309
Sivanandan, R., 1241
Slaaf, D. W., 816
Slamon, D. J., 412
Slavin, J., 679
Slooter, G. D., 31
Smedh, K., 273
Smeets, H. J., 693
Smith, A. M., 564
Smith, C. D., 1649
Smith, I. C. P., 1234
Smith, W. C. S., 1122
Smout, A. J. P. M., 569
So, J. B. Y., 45
Soh, J. G. S., 801
Sola, A., 1366
Sommacale, D., 73
Somorjai, R. L., 1234
Soo, K. C., 1241
Souza, D. S. R., 1209
Spark, J. I., 382, 1583
Spitzer, W. J., 450
Stansby, G., 787
Statius Muller, M. G., 539
Steele, R. J. C., 1617
Steens, J., 1492
Stengel, D., 901
Straathof, J. W. A., 1519
Stratford, J., 577
Stringer, M. D., 878
Stromqvist, M., 286
Stroosma, O. B., 500
Sturgeon, C. M., 255
Subba Rao, K. V., 1602
Sudhindran, S., 1178
Sugimachi, K., 1463
Sugimachi, K., 59
Sugimasa, Y., 1596
Suleman, B. A., 206
Susarla, P., 393
Sutton, G. L., 958
Svendsen, F., 1001
Swift, R. I., 1628
Syk, I., 228

Tabar, L., 1513
Tachimori, Y., 439
Taha, R., 261
Tai, B.-C., 801
Tait, D. M., 1628
Takahashi, A., 1110
Takahashi, H., 364
Takala, A., 222
Takala, J., 1006
Takanashi, Y., 1596

Takemiya, S., 1596
Takenaka, K., 1463
Takenoshita, S., 704
Talamini, G., 376, 419
Tam, P. K. H., 545
Tambiah, J., 935
Tan, B., 246
Tang, C.-L., 357, 801
Taniura, H., 515
Taylor, A. L., 724
Taylor, A. M., 1077
Taylor, I., 176
Taylor, P. R., 389
Taylor, R., 860
Terkivatan, T., 207
Thomas, D. G., 687
Thomas, M. L., 629
Thomas, P. K., 545
Thomas, S., 393
Thompson, E., 577
Thompson, M. H., 65
Thörn, M., 1644
Tiebosch, A., 1201
Tilanus, H. W., 207, 715, 1578
Todd, S., 662
Todoroki, T., 364
Toh, S., 216
Tollenaar, R. A. E. M., 693
Tomezzoli, A., 419
Tranter, S. E., 65
Travis, S. J., 77
Tremayne, A. B., 1099
Trendell-Smith, N., 935
Troxler, M., 1169
Trus, T. L., 1649
Tsai, Y.-C., 986
Tsang, C., 1449
Tsavellas, G., 1307
Tsuchiya, A., 704
Tsui, J. C. S., 1209
Tsuji, T., 831
Tulchinsky, H., 1602

Uchida, M., 515
Uenishi, T., 969
Ueno, H., 994
Uesaka, K., 1084
Uhl, W., 975
Uitdehaag, B. M. J., 1285
Ung, O., 860
Unnikrishnan, M., 536
Uzunkoy, A., 85

Vaizey, C. J., 1037
Valls, C., 980
Vammen, S., 1066
van Beek, M. W. P. M., 163
van Coevorden, F., 458
van de Velde, C. J. H., 267, 1556

van de Watering, L. M. G., 267
van den Broek, W. T., 251
van den Dungen, J., 1201
van den Dungen, J. J. A. M., 1382
van den Tol, M. P., 1258
van der Bij, W., 433
van der Hem, J. A., 884
van der Sangen, M. J. C., 118
van der Want, J., 1201
van Eijck, M., 31
van Engelshoven, J. M. A., 1506
van Geenen, R. C. I., 1467
van Geldere, D., 1285
van Gulik, T. M., 48, 1467
van Hogezand, R. A., 1492
van Laarhoven, C. J. H. M., 241
Van Lanschot, J. J. B., 715
van Leeuwen, P. A. M., 539
van Poll, D., 305
van Rijn, R. R., 207
van Rossen, M. E. E., 1258
Van Sandick, J. W., 715
Van Schaardenburgh, P., 693
van Schilfgaarde, R., 1201
van Slooten, G. W., 458
Vanamo, K., 510
Vauthey, J. N., 165, 325
Velayudham, M., 1539
Vermey, A., 1382
Visvikis, D., 176
Vlahakes, G. J., 1553
von Blomberg, B. M. E., 539
Voogd, A. C., 118
Vos, P., 48
Vowden, P., 382
Vural, H., 85

Waddell, I., 588
Wakai, T., 675
Waller, J. R., 1429
Wallin, G., 557
Walsh, S., 114
Walsh, T. N., 1105
Wang, J. H., 246
Wang, Y., 825
Wängberg, B., 865
Wara, P., 200
Wastell, C., 298
Watanabe, G., 426
Watanabe, H., 439, 675
Watanabe, T., 704
Watkins, P. E., 22
Watson, C. J. E., 1330
Watson, D. I., 1117, 1296
Watson, H. R., 1376
Watson, S. A., 564
Wattchow, D. A., 931
Weber, G., 557
Wehrens, X. H. T., 816
Welsh, K. I., 1330
Wemyss-Holden, S. A., 1442
Westberg, G., 865
Whatling, P. J., 814
Whitman, B., 1344
Whyman, M. R., 941
Wichmann, M. W., 1092
Wigmore, S. J., 255
Wijeyaratne, S. M., 951
Wijnhoven, B. P. L., 569
Wikman, F. P., 1228
Wild, A., 1403
Wilkinson, A. R., 1590
Wilkinson, D., 382
Wilkinson, K. H., 1602
Wille-Jørgensen, P., 1413
Willetts, I. E., 878
Williams, A. B., 853
Williams, J., 1602
Williams, N. S., 405, 545
Williamson, R. C. N., 1189
Wills, V. L., 486
Windmill, D. C., 261
Witkamp, A. J., 458
Wobbes, T., 643, 844
Wolfe, J. H., 523
Wolff, B. G., 771
Woodburn, K. R., 77
Worni, M., 975
Wu, C.-C., 210
Wu, Q. D., 246

Xaus, C., 1366

Yamada, K., 988
Yamaguchi, H., 439
Yamamoto, T., 969
Yamanoi, A., 515
Yamashita, Y., 1463
Yamazaki, O., 969
Yanaga, K., 59
Yang, H.-K., 1408
Yanoma, S., 1596
Yasuda, K., 873
Yeh, D.-C., 210
Yokoyama, N., 675
Yoshikawa, T., 1596
Young, A. E., 1027
Yukawa, N., 1596

Z'graggen, K., 1501
Zamboni, F., 1194
Zamboni, G., 376
Zedenius, J., 557
Zeebregts, C., 1201
Zeeh, J., 90
Zippel, K., 99
Zoetmulder, F. A. N., 458

Index to Volume 88

Subject index

Adhesion
Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth, 1258
Reduction of experimental adhesion formation by inhibition of plasminogen activator inhibitor type 1, 286
The intestinal flora influences adhesion formation around surgical anastomoses, 143

AIDS
Incidence of acquired immune deficiency syndrome (AIDS)-related disorders at laparotomy in patients with AIDS, 294

Amputation
Revisiting transtibial amputation with the long posterior flap, 683
Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates, 529

Anal canal
Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging, 1506

Anastomosis
Systematic review of definition and measurement of anastomotic leak after gastrointestinal surgery, 1157

Aneurysm
Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre, 1341
Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms, 1472
Endovascular treatment of abdominal aortic aneurysm: a failed experiment, 1281
Epidemiology of abdominal aortic aneurysm in the Asian community, 382
In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthetic Society audit, 687
Management of aortic aneurysm in the presence of a horseshoe kidney, 500
Performance indicators from routine hospital data: death following aortic surgery as a potential measure of quality of care, 964
Portsmouth POSSUM models for abdominal aortic aneurysm surgery, 958
Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm, 1335
Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae*, 935
Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion, 1066
Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair, 1059
Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery, 1583
Screening for abdominal aortic aneurysm, 625
A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men, 941
Suitability for endovascular aneurysm repair in an unselected population, 77

Angiogenesis
Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease, 945

Anorectal
Transvaginal repair of pouch–vaginal fistula, 241

Anorectal physiology
Function of colonic J pouch continues to improve with time, 1623

Antibiotics
Systematic review of antimicrobial agents for chronic wounds, 4

Anus
Anorectal injury following pelvic radiotherapy, 1037

Aorta
Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre, 1341
Comparison of cardiac troponin 1 and creatine kinase ratios in the detection of myocardial injury after aortic surgery, 1196
Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms, 1472
Endovascular treatment of abdominal aortic aneurysm: a failed experiment, 1281
Epidemiology of abdominal aortic aneurysm in the Asian community, 382
Fate of hypertension after repair of coarctation of the aorta in adults, 536
In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthetic Society audit, 687
Management of aortic aneurysm in the presence of a horseshoe kidney, 500
Penetrating atherosclerotic ulcers of the aorta, 1169
Performance indicators from routine hospital data: death following aortic surgery as a potential measure of quality of care, 964
Portsmouth POSSUM models for abdominal aortic aneurysm surgery, 958
Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm, 1335
Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae*, 935
Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion, 1066
Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair, 1059
Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery, 1583

Screening for abdominal aortic aneurysm, 625
Suitability for endovascular aneurysm repair in an unselected population, 77

Appendicectomy
Suspected acute appendicitis: trends in management over 30 years, 1570

Appendicitis
Suspected acute appendicitis: trends in management over 30 years, 1570

Appendix
Conservative management of appendix mass in children, 1539
A normal appendix found during diagnostic laparoscopy should not be removed, 251
Randomized clinical trial of laparoscopic *versus* open appendicectomy, 200
Randomized study to examine the value of on-table inspection of the appendix mucosa (short note), 837
Single-blind randomized clinical trial of laparoscopic *versus* open appendicectomy in children, 510
Small bowel obstruction after appendicectomy, 1387

Arterial – disease
Reintervention as a clinical trial endpoint after peripheral arterial bypass surgery, 1376
Revisiting transtibial amputation with the long posterior flap, 683
Sympathetic autoregulation in peripheral vascular disease, 523
Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease, 787
Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates, 529

Arterial – surgery
Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery, 1196
Fate of hypertension after repair of coarctation of the aorta in adults, 536
Reintervention as a clinical trial endpoint after peripheral arterial bypass surgery, 1376
Risk modelling study for carotid endarterectomy, 1590
Use of cadaveric superior mesenteric artery as interpositional vascular graft in orthotopic liver transplantation, 70

Atheroma
Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease, 945
Differences in the detection of cyclo-oxygenase 1 and 2 proteins in symptomatic and asymptomatic carotid plaques, 951

Audit
Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre, 1341
In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthetic Society audit, 687
Outcome and resource utilization in gastroenterological surgery, 1006
Performance indicators from routine hospital data: death following aortic surgery as a potential measure of quality of care, 964
Portsmouth POSSUM models for abdominal aortic aneurysm surgery, 958
Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit, 273
Standards of documentation of the surgeon–patient consultation in current surgical practice, 309
Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark, 1413
Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note), 1344

Axilla
Botulinum toxin injection is an effective treatment for axillary hyperhidrosis (short note), 814

Bacteria
Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae*, 935

Bile
Haemobilia, 773

Bile duct
Non-operative management of haemobilia, 1073
Potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile duct stones, 65

Bile duct – surgery
Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma, 1463

Bile duct – tumour
Incidence of benign lesions in patients resected for suspicious hilar obstruction, 48
Treatment strategy for patients with middle and lower third bile duct cancer, 364
Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma, 1463

Blood
Haemobilia, 773

Bowel disorders
Preliminary study of D-dimer as a possible marker of acute bowel ischaemia, 385

Breast
Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer, 118
Impact of mammographic interval on stage and survival after the diagnosis of contralateral breast cancer, 123

Breast – malignant
Blockade of growth factor receptors in ductal carcinoma *in situ* inhibits epithelial proliferation, 412
Diagnosis and prognosis of breast cancer by magnetic resonance spectroscopy of fine-needle aspirates analysed using a statistical classification strategy, 1234

Estimating the benefits of adjuvant systemic therapy for women with early breast cancer, 1513

Breast – surgery
Endoscopic axillary surgery in breast cancer, 698
Prospective evaluation of the morbidity of axillary clearance for breast cancer, 114
Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection, 1639

Breast – tumour
Extent of ductal carcinoma *in situ* within the surrounding invasive primary breast carcinoma, 1324
Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer, 1644
Probability of axillary node involvement in patients with tubular carcinoma of the breast, 860
Prospective evaluation of the morbidity of axillary clearance for breast cancer, 114
Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer, 704
Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection, 1639

Burn
Determinants of death following burn injury, 583

Calculus
Potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile duct stones, 65

Carcinoid
Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome, 865

Cardiothoracic
Preserved endothelial integrity and nitric oxide synthase in saphenous grafts harvested by a 'no-touch' technique, 1209

Carotid
Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease, 945
Differences in the detection of cyclo-oxygenase 1 and 2 proteins in symptomatic and asymptomatic carotid plaques, 951
Outcome of surgical treatment for carotid body paraganglioma, 1382
Risk modelling study for carotid endarterectomy, 1590
Value of intraoperative duplex imaging during supervised carotid endarterectomy, 389

Carotid body tumours
Outcome of surgical treatment for carotid body paraganglioma, 1382

Chemotherapy
Estimating the benefits of adjuvant systemic therapy for women with early breast cancer, 1513

Colon
Irritable bowel syndrome: new horizons in pathophysiology and treatment, 1425
Scintigraphic assessment of colonic transit in women with slow-transit constipation arising *de novo* following pelvic surgery or childbirth, 405

Colon – general
Decreased tyrosine kinase C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic slow-transit constipation, 545

Colon – inflammatory
Diverticular disease of the colon in Accra, Ghana (short note), 1595
Experimental sodium phosphate and polyethylene glycol induce colonic tissue damage and oxidative stress, 85
Immune therapy in inflammatory bowel disease and models of colitis, 1558
Tumour necrosis factor inhibitors reduce the acute-phase response in hapten-induced colitis, 235

Colon – miscellaneous
Irritable bowel syndrome: new horizons in pathophysiology and treatment, 1425

Colon – surgery
'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery, 1533
Function of colonic J pouch continues to improve with time, 1623
Inhibition of matrix metalloproteinases enhances breaking strength of colonic anastomoses in an experimental model, 228
Insulin-like growth factor I and truncated keratinocyte growth factor accelerate healing of left-sided colon anastomoses, 90
Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative, 1498
Prospective study of primary anastomosis following sigmoid resection for suspected acute complicated diverticular disease, 693
Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma, 1216
Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery, 1363
Strategy for the surgical management of patients with idiopathic megarectum and megacolon, 1392
Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery, 1501
Use of a minilaparotomy in the treatment of colonic cancer, 831

Colon – tumour
Acute-phase protein response, survival and tumour recurrence in patients with colorectal cancer, 255
Detection and clinical significance of occult tumour cells in colorectal cancer, 1307
Gender differences in long-term survival of patients with colorectal cancer, 1092
High-risk colorectal adenomas and serum insulin-like growth factors, 107
Immune-stimulating effects of low-dose, perioperative recombinant granulocyte–macrophage colony-stimulating facto treatment in patients operated on for primary colorectal carcinoma, 539
Long-term results of treating hepatic colorectal liver metastases with cryosurgery, 844
Non-invasive methods of assessing angiogenesis and their value i predicting response to treatment in colorectal cancer, 1628

Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer, 1352
Patient accuracy of reporting on hereditary non-polyposis colorectal cancer-related malignancy in family members, 1228
Plasma concentration of tissue inhibitor matrix metalloproteinase 1 in patients with colorectal carcinoma, 1596
Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma, 1216
Randomized clinical trial of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer, 801
Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit, 273
Sodium hyaluronate enhances colorectal tumour cell metastatic potential *in vitro* and *in vivo*, 246
Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery, 1501
Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer, 839
Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer, 101

Coloproctology
Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy, 853
Ileoanal pouch function is related to postprandial pouch tone, 1492
Systemic levels of glyceryl trinitrate following topical applications to the anoderm do not correlate with the measured reduction in anal pressure, 1613
Topical diltiazem ointment in the treatment of chronic anal fissure, 553

Colostomy
Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized controlled trial, 360

Constipation
Ileal neoappendicostomy for antegrade colonic irrigation (short note), 1637

Crohn's disease
Resection margins in Crohn's disease, 771

Cytology
Detection and clinical significance of occult tumour cells in colorectal cancer, 1307

Diverticulum
Oesophageal diverticula, 629

Dysphagia
Analysis and surgical treatment of persistent dysphagia after Nissen fundoplication, 569
Dysphagia after antireflux surgery, 486

Embolization
Portal vein embolization: rationale, technique and future prospects, 165

Endocrine
Phaeochromocytoma in pregnancy, 481
Prospective controlled trial of standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1, 1403
Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours, 31

Endocrine – adrenal
Phaeochromocytoma in pregnancy, 481

Endoscopy - ERCP
Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis, 1178

Epidemiology
Epidemiological study of oesophageal and gastric cancer in the south-east of England, 1249
Epidemiology of abdominal aortic aneurysm in the Asian community, 382
One-year survey of carcinoma of the oesophagus and stomach in Wales, 278

Ethics
Confidentiality and healthcare, 1155
Ethics of consent to surgical treatment, 1283
Ethics of surgical innovation, 897
Ethics in surgical practice, 769
Medical negligence and the law, 899
Postoperative futility: a clinical algorithm for setting limits, 1153

Experimental
Effect of $CD4^+$ and $CD8^+$ cell depletion on wound healing, 298
Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation, 1366
Experimental models of Gram-negative sepsis, 22
Experimental sodium phosphate and polyethylene glycol induce colonic tissue damage and oxidative stress, 85
Experimental study of type 3 phosphodiesterase inhibitor on liver graft function, 59
Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth, 1258
Insulin-like growth factor I and truncated keratinocyte growth factor accelerate healing of left-sided colon anastomoses, 90
The intestinal flora influences adhesion formation around surgical anastomoses, 143
Local heat-shock priming-induced improvement in microvascular perfusion in osteomyocutaneous flaps is mediated by heat-shock protein 32, 450
Microcirculatory effects of experimental acute limb ischaemia–reperfusion, 816
Preservation of endothelial integrity and function in experimental vascular anastomoses using non-penetrating clips, 1201
Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae*, 935
Recombinant soluble P-selectin glycoprotein ligand 1 moderates local and remote injuries following experimental lower-torso ischaemia, 825
Reduction of experimental adhesion formation by inhibition of plasminogen activator inhibitor type 1, 286

Sodium hyaluronate enhances colorectal tumour cell metastatic potential *in vitro* and *in vivo*, 246

Fissure
Topical diltiazem ointment in the treatment of chronic anal fissure, 553

Fistula
Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized clinical trials, 190
Transvaginal repair of pouch–vaginal fistula, 241

Fundoplication
Analysis and surgical treatment of persistent dysphagia after Nissen fundoplication, 569

Gallbladder
Early gallbladder carcinoma does not warrant radical resection, 675
Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy, 1001
Randomized trial of needlescopic *versus* laparoscopic cholecystectomy, 45

Gastric
Expression of gastrin in developing gastric adenocarcinoma, 564
Percutaneous endoscopic gastrostomy in patients with ventriculoperitoneal shunts, 724
Randomized clinical trial of *Helicobacter pylori* from dental plaque (short note), 206
Systematic review of definition and measurement of anastomotic leak after gastrointestinal surgery, 1157

Gastric – cancer
Laparoscopically assisted total or distal gastrectomy with lymph node dissection for early gastric cancer, 128

General
Confidentiality and healthcare, 1155
Doctors and the law – a personal view, 1025
Ethics of consent to surgical treatment, 1283
Ethics of surgical innovation, 897
Ethics in surgical practice, 769
Haemoglobin solutions in surgery, 1553
Medical negligence and the law, 899
Postoperative futility: a clinical algorithm for setting limits, 1153
Probiotics, 161
Risk management, 1027

Genetics
Patient accuracy of reporting on hereditary non-polyposis colorectal cancer-related malignancy in family members, 1228

Graft
Preserved endothelial integrity and nitric oxide synthase in saphenous grafts harvested by a 'no-touch' technique, 1209

Haemorrhoids
Follow-up confirms sustained benefit of circumferential stapled anoplasty in the management of prolapsing haemorrhoids, 850
Long-term effects of stapled haemorrhoidectomy on internal anal function and sensitivity, 1487
Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy, 669
Randomized clinical trial of stapled *versus* Milligan–Morgan haemorrhoidectomy, 1049
Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy, 1449
Stapled haemorrhoidectomy: pain or gain, 1

Hernia
Chronic pain and quality of life following inguinal hernia repair, 1122
Contralateral groin exploration is not justified in infants with a unilateral inguinal hernia, 720
Cost-utility analysis of open *versus* laparoscopic groin hernia repair: results from a multicentre randomized clinical trial, 653
Prospective randomized trial of polypropylene mesh compared with nylon darn in inguinal hernia repair, 931
Randomized clinical trial comparing totally extraperitoneal inguinal hernia repair with the Shouldice technique, 1183
Totally extraperitoneal endoscopic repair of recurrent inguinal hernia, 884

Hernia – hiatus
Role of fundoplication in patient symptomology after laparoscopic antireflux surgery, 1117

Hernia – umbilical
Randomized clinical trial comparing suture and mesh repair of umbilical hernia in adults, 1321

HIV
Incidence of acquired immune deficiency syndrome (AIDS)-related disorders at laparotomy in patients with AIDS, 294

Hyperparathyroidism
Unique clinical characteristics of primary hyperparathyroidism in India, 708

Ileostomy
Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized controlled trial, 360

Imaging
Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging, 1506
Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy, 853
Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours, 31
Value of intraoperative duplex imaging during supervised carotid endarterectomy, 389

Immune system
Effect of laparoscopy on immune function, 1296

Immunology
Effects of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes, 1110

Incontinence
Clinical and economic evaluation of surgical treatments for faecal incontinence, 1029
Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence, 1481

Intestinal
Nitric oxide prevents intestinal mitochondrial dysfunction induced by surgical stress, 393
Systematic review of definition and measurement of anastomotic leak after gastrointestinal surgery, 1157

Intussusception
Endotoxin, cytokines and lipid peroxidases in children with intussusception, 878

Ischaemia
Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation, 1366
Expression of inducible nitric oxide synthase contributes to the development of pancreatitis following pancreatic ischaemia and reperfusion, 1189
Microcirculatory effects of experimental acute limb ischaemia–reperfusion, 816
Preliminary study of D-dimer as a possible marker of actute bowel ischaemia, 385
Recombinant soluble P-selectin glycoprotein ligand 1 moderates local and remote injuries following experimental lower-torso ischaemia, 825
Role of tumour necrosis factor in lung injury caused by intestinal ischaemia–reperfusion, 464
Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note), 1344

Isotope
Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours, 31

Kidney
Management of aortic aneurysm in the presence of a horseshoe kidney, 500

Laparoscopy
Effect of laparoscopy on immune function, 1296
Impact of laparoscopic surgery on experimental hepatic metastases, 371
Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus, 577
A normal appendix found during diagnostic laparoscopy should not be removed, 251
Prospective study of the effect of laparoscopic Nissen fundoplication on reflux mechanisms, 1519
Randomized clinical trial of laparoscopic *versus* open appendicectomy, 200
Randomized clinical trial of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer, 801
Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy, 1001
Randomized trial of needlescopic *versus* laparoscopic cholecystectomy, 45
Selection of patients for laparoscopic repair of perforated peptic ulcer, 133
Single-blind randomized clinical trial of laparoscopic *versus* open appendicectomy in children, 510
Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark, 1413
Totally extraperitoneal endoscopic repair of recurrent inguinal hernia, 884

Laparoscopy – lower GI
Blinded prospective study of the incidence of deep venous thrombosis following conventional or laparoscopic colorectal resection (short note), 99

Laparoscopy – upper GI
Laparoscopically assisted total or distal gastrectomy with lymph node dissection for early gastric cancer, 128
Laparoscopy in the staging of pancreatic cancer, 325
Potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile duct stones, 65

Laparotomy
Randomized clinical trial of local bupivacaine perfusion *versus* parenteral morphine infusion for pain relief after laparotomy, 357

Law and ethics
Doctors and the law – a personal view, 1025

Liver – malignant
Liver transplantation for early-detected, multifocal hepatocellular carcinoma (short note), 1194

Liver – metastases
An unexpected liver secondary, 627
Rectal adenocarcinoma with liver metastases: management of the primary tumour, 163

Liver – surgery
Improving operative safety for cirrhotic liver resection, 210
Liver regeneration after major hepatectomy for biliary cancer, 1084
Management of 155 patients with benign liver tumours, 808
Postoperative liver function after elective right hepatecotomy in elderly patients, 73

Liver – transplantation
Experimental study of type 3 phosphodiesterase inhibitor on liver graft function, 59
Liver transplantation for early-detected, multifocal hepatocellular carcinoma (short note), 1194
The National Liver Transplantation Audit: an overview of patients presenting for liver transplantation from 1994 to 1998, 52
Use of cadaveric superior mesenteric artery as interpositional vascular graft in orthotopic liver transplantation, 70

Liver – trauma
Haemobilia, 773

Liver – tumour
Clinicopathological study of hepatocellular carcinoma with diaphragmatic involvement (short note), 681

Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma, 969
Gamma-glutamyl transpeptidase messenger RNA may serve as a diagnostic aid in hepatocellular carcinoma (short note), 986
Liver transplantation for early-detected, multifocal hepatocellular carcinoma (short note), 1194
Long-term results of treating hepatic colorectal liver metastases with cryosurgery, 844
Management of 155 patients with benign liver tumours, 808
Postoperative liver function after elective right hepatectomy in elderly patients, 73
Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis, 515
Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal metastases, 980
Treatment of ruptured hepatocellular adenoma, 207

Lung
Role of tumour necrosis factor in lung injury caused by intestinal ischaemia–reperfusion, 464

Lymph node
Lymph node micrometastasis and prognosis in patients with oesophageal squamous cell carcinoma, 426
Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer, 1644
Prospective analysis of the diagnostic yield of extended *en bloc* resection for adenocarcinoma of the oesophagus or gastric cardia, 715
Sentinel lymph node biopsy in the management of thyroid disease, 321
Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer, 704
Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection, 1639

Lymph system – surgery
Management of thoracic duct injuries after oesophagectomy, 1442

Management
Analysis of local recurrence and optimizing excision margins for cutaneous melanoma, 137
Clinical and economic evaluation of surgical treatments for faecal incontinence, 1029
Irritable bowel syndrome: new horizons in pathophysiology and treatment, 1425
Management of aortic aneurysm in the presence of a horseshoe kidney, 500
Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery, 913
Probiotics, 161
Provision of long-term vascular access for haemodialysis in a patient with exhausted superficial arm veins, 484
Sentinel lymph node biopsy in the management of thyroid disease, 321
Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized clinical trials, 190
Suspected acute appendicitis: trends in management over 30 years, 1570
Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease, 787
Systematic review of randomized clinical trials of surgical treatment for carpal tunnel syndrome, 1285
Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates, 529
Varicose veins and pregnancy, 323

Melanoma
Analysis of local recurrence and optimizing excision margins for cutaneous melanoma, 137
Sentinel nodes outside lymph node basins in patients with melanoma, 305

Metabolism
Leptin and its relation to weight loss, *ob* gene expression and the acute-phase response in surgical patients, 588

Metastasis
Long-term results of treating hepatic colorectal liver metastases with cryosurgery, 844

Morbidity
Prospective evaluation of the morbidity of axillary clearance for breast cancer, 114

MRI
Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy, 853

Nutrition
Percutaneous endoscopic gastrostomy in patients with ventriculoperitoneal shunts, 724
Randomized clinical trial of patient-controlled *versus* fixed regimen feeding after elective abdominal surgery, 1578

Obesity
Intragastric balloon in the treatment of patients with morbid obesity, 1245

Obstruction
Small bowel obstruction after appendicectomy, 1387

Oesophagus
Oesophageal diverticula, 629
Prospective analysis of the diagnostic yield of extended *en bloc* resection for adenocarcinoma of the oesophagus or gastric cardia, 715

Oesophagus – inflammatory
Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus, 577
Prospective study of the effect of laparoscopic Nissen fundoplication on reflux mechanisms, 1519
Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery, 1649
Role of fundoplication in patient symptomology after laparoscopic antireflux surgery, 1117

Oesophagus – surgery
Diagnosis and management of a mediastinal leak following radical oesophagectomy, 1346
Dysphagia after antireflux surgery, 486
Management of thoracic duct injuries after oesophagectomy, 1442
Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery, 1649

Oesophagus – tumour
Diagnosis and management of a mediastinal leak following radical oesophagectomy, 1346
Effect of multimodality therapy on circulating vascular endothelial growth factor levels in patients with oesophageal cancer, 1105
Effects of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes,1110
Epidemiological study of oesophageal and gastric cancer in the south-east of England, 1249
One-year survey of carcinoma of the oesophagus and stomach in Wales, 278
Other primary cancers occurring after treatment of superficial oesophageal cancer, 439
Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer, 338
Prevention of the neoplastic progression of Barrett's oesophagus by endoscopic argon beam plasma ablation, 1357

Oncology
Analysis of local recurrence and optimizing excision margins for cutaneous melanoma, 137
Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei, 458
Quality of life as an outcome measure in surgical oncology, 643

Orthopaedic
Systematic review of randomized clinical trials of surgical treatment for carpal tunnel syndrome, 1285

Paediatrics
Conservative management of appendix mass in children, 1539
Decreased tyrosine kinase C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic slow-transit constipation, 545

Pain
Randomized clinical trial of local bupivacaine perfusion *versus* parenteral morphine infusion for pain relief after laparotomy, 357

Pancreas
Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized clinical trials, 190

Pancreas – cancer
Experience with laparoscopic ultrasonograpy for defining tumour resectability in carcinoma of the pancreatic head and periampullary region, 1077

Pancreas – inflammatory
Activation peptide of carboxypeptidase B and anionic trypsinogen as early predictors of the severity of acute pancreatitis, 216
Expression of inducible nitric oxide synthase contributes to the development of pancreatitis following pancreatic ischaemia and reperfusion, 1189
Late mortality in patients with severe acute pancreatitis, 975
Plasma trypsinogen activation peptide in patients with acute pancreatitis (short note), 679
Procalcitonin strip test in the early detection of severe acute pancreatitis, 222
Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis, 1178
Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized clinical trials, 190

Pancreas – malignant
Laparoscopy in the staging of pancreatic cancer, 325

Pancreas – surgery
Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas, 376
Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy, 1456
Readmissions after pancreatoduodenectomy, 1467

Pancreas – transplantation
Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation, 1366

Pancreas – tumour
Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas, 376
Laparoscopy in the staging of pancreatic cancer, 325
Prospective controlled trial of standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1, 1403
Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy, 1456
Randomized, dose-finding phase III study of lithium gamolenate in patients with advanced pancreatic adenocarcinoma, 662

Peptic ulcer
Effect of *Helicobacter pylori* eradication on the ulcer recurrence rate after simple closure of perforated duodenal ulcer: retrospective and prospective randomized controlled studies, 1054
Selection of patients for laparoscopic repair of perforated peptic ulcer, 133

Peritoneum
Response of visceral peritoneum to abdominal surgery, 148

Portal vein
Portal vein embolization: rationale, technique and future prospects, 165

Pouch
Ileoanal pouch function is related to postprandial pouch tone, 1492

Prophylaxis
Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery, 913

Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion, 1066

Quality of life
Chronic pain and quality of life following inguinal hernia repair, 1122
Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer, 1617
Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma, 1216
Quality of life as an outcome measure in surgical oncology, 643

Radiology – interventional
Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm, 1335
Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair, 1059
Suitability for endovascular aneurysm repair in an unselected population, 77

Radiology – PET
Positron emission tomography and colorectal cancer, 176

Radiotherapy
Anorectal injury following pelvic radiotherapy, 1037
Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer, 338
Preoperative radiotherapy for rectal cancer, 1556
Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer, 839

Rectum
Anorectal injury following pelvic radiotherapy, 1037
Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer, 839

Rectum – cancer
Detection and clinical significance of occult tumour cells in colorectal cancer, 1307
Positron emission tomography and colorectal cancer, 176
Preoperative radiotherapy for rectal cancer, 1556
Rectal adenocarcinoma with liver metastases: management of the primary tumour, 163
Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit, 273

Rectum – surgery
Impact of total mesorectal excision on the results of surgery of distal rectal cancer, 1607
Methodology and reporting in studies of local recurrence after curative excision of the rectum for cancer, 1476
Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence, 1481
Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer, 400
Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer, 1221
Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer, 1617
Salvage abdominal surgery in patients with a retained rectal stump after restorative proctocolectomy and stapled anastomosis, 1602
Strategy for the surgical management of patients with idiopathic megarectum and megacolon, 1392
Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery, 1501

Rectum – tumour
Criteria for extramural perineural invasion as a prognostic parameter in rectal cancer, 994
Detection and clinical significance of occult tumour cells in colorectal cancer, 1307
High-risk colorectal adenomas and serum insulin-like growth factors, 107
Hospital caseload and the results achieved in patients with rectal cancer, 1397
Immune-stimulating effects of low-dose, perioperative recombinant granulocyte–macrophage colony-stimulating factor treatment in patients operated on for primary colorectal carcinoma, 539
Impact of total mesorectal excision on the results of surgery of distal rectal cancer, 1607
Methodology and reporting in studies of local recurrence after curative excision of the rectum for cancer, 1476
Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer, 1352
Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer, 988
Plasma concentration of tissue inhibitor matrix metalloproteinase 1 in patients with colorectal carcinoma, 1596
Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer, 1221
Preoperative radiotherapy for rectal cancer, 1556
Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer, 1617
Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery, 1501

Renal transplantation
Influence of aspirin on early allograft thrombosis and chronic allograft nephropathy following renal transplantation, 261
Molecular mechanisms of renal allograft fibrosis, 1429

Screening
Impact of mammographic interval on stage and survival after the diagnosis of contralateral breast cancer, 123
Screening for abdominal aortic aneurysm, 625

Sepsis
Experimental models of Gram-negative sepsis, 22
Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery, 1583

Small bowel – inflammatory
Immune therapy in inflammatory bowel disease and models of colitis, 1558

Sphincter
Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy, 853

Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence, 1481

Stomach – cancer
Clinical significance of mutator phenotype and chromosome 17p and 18q allelic loss in gastric cancer, 419

Stomach – surgery
Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer, 444
Risk factors for complications following resection of large gastric cancer, 873

Stomach – tumour
Epidemiological study of oesophageal and gastric cancer in the south-east of England, 1249
Expression of gastrin in developing gastric adenocarcinoma, 564
Influence of the number of lymph nodes examined on staging of gastric cancer, 1408
Lymph node micrometastasis and prognosis in patients with oesophageal squamous cell carcinoma, 426
One-year survey of carcinoma of the oesophagus and stomach in Wales, 278
Risk factors for complications following resection of large gastric cancer, 873

Surgical technique
Resection margins in Crohn's disease, 771
Revisiting transtibial amputation with the long posterior flap, 683
Stapled haemorrhoidectomy: pain or gain, 1

Surgical training
Training in infrainguinal bypass surgery for severe leg ischaemia, 82
Validity of surgical simulation for the assessment of operative skill, 1525

Sympathetic
Sympathetic autoregulation in peripheral vascular disease, 523

Thoracic
Management of thoracic duct injuries after oesophagectomy, 1442

Thrombolytic therapy
Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note), 1344

Thrombosis
Influence of aspirin on early allograft thrombosis and chronic allograft nephropathy following renal transplantation, 261

Thyroid
Expression of the *RET* proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome, 557
Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid, 1241
Sentinel lymph node biopsy in the management of thyroid disease, 321

Transfusion
Haemoglobin solutions in surgery, 1553
Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence, 267

Transit
Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative, 1498

Transplantation – kidney
Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients, 1330

Transplantation – miscellaneous
Gastrointestinal complications in lung transplant survivors that require surgical intervention, 433

Trauma
Road traffic fatalities in Victoria, Australia and changes to the trauma care system, 1099

Trauma – blunt
Systematic review and meta-analysis of emergency ultrasonography for blunt abdominal trauma, 901

Ulcer
Penetrating atherosclerotic ulcers of the aorta, 1169

Ultrasonography
Potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile duct stones, 65
A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men, 941
Systematic review and meta-analysis of emergency ultrasonography for blunt abdominal trauma, 901

Urology
Review of current practice to establish success after vasectomy, 290

Varicose veins
Varicose veins and pregnancy, 323

Vascular access
Provision of long-term vascular access for haemodialysis in a patient with exhausted superficial arm veins, 484

Vascular surgery
Preservation of endothelial integrity and function in experimental vascular anastomoses using non-penetrating clips, 1201
Training in infrainguinal bypass surgery for severe leg ischaemia, 82

Vein
Present and future management of deep vein thrombosis, 1427
Preserved endothelial integrity and nitric oxide synthase in saphenous grafts harvested by a 'no-touch' technique, 1209

Venous thrombosis
Blinded prospective study of the incidence of deep venous thrombosis following conventional or laparoscopic colorectal resection (short note), 99
Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery, 913
Present and future management of deep vein thrombosis, 1427

Wound closure
Double near and far Prolene suture closure: a technique for abdominal wall closure after laparostomy (short note), 146

Wound healing
Effect of $CD4^+$ and $CD8^+$ cell depletion on wound healing, 298
Inhibition of matrix metalloproteinases enhances breaking strength of colonic anastomoses in an experimental model, 228
Insulin-like growth factor I and truncated keratinocyte growth factor accelerate healing of left-sided colon anastomoses, 90
Local heat-shock priming-induced improvement in microvascular perfusion in osteomyocutaneous flaps is mediated by heat-shock protein 32, 450
Randomized clinical trial of diathermy *versus* scalpel incision in elective midline laparotomy, 41
Systematic review of antimicrobial agents for chronic wounds, 4

The Editors are grateful to the following reviewers for refereeing papers in the year to 30 September 2001

Abercrombie, J. F.
Abulafi, A.
Aitken, R. J.
Akerström, G.
Akyol, M.
Alderson, D.
Aldridge, M. C.
Alexander, J.
Allardice, J. T.
Allen-Mersh, T. G.
Allison, D. J.
Allison, S. P.
Allo, M. D.
Allum, W. H.
Altomare, D. F.
Amid, P. K.
Anderson, I.
Anderson, J. H.
Anderson, J. R.
Angelini, G.
Archer, T. J.
Armitage, N. C.
Armstrong, C. P.

Bachmann, M.
Backdahl, M.
Baeten, C. G. M. I.
Baigrie, R. J.
Baildam, A.
Bailey, I.
Baird, R. N.
Baker, D.
Bancewicz, J.
Bannister, G.
Barham, C. P.
Barlow, A. P.
Barr, H.
Barr, L. C.
Barros D'Sa, A. A. B.
Barry, R. E.
Bartels, H.
Bartolo, D. C. C.
Bartram, C. I.
Baskerville, P. A.
Bassi, C.
Baston, J.
Bates, T.
Baum, M.
Baxter, J. N.
Beard, J. D.
Beart, R. W.
Beckingham, I. J.
Beechey-Newman, N.
Beets, G. L.
Beger, H. G.
Belghiti, J.
Bell, P. R. F.
Bellamy, M.
Bemelmans, M. H. A.
Bengmark, S.
Bennett, I. C.
Bergenfelz, A.
Bergqvist, D.
Berridge, D. C.
Berry, A. R.
Beynon, J.
Blazeby, J. M.
Blichert-Toft, M.
Blumgart, L. H.
Boey, J.
Bonavina, L.
Bonjer, H. J.
Bornman, P. C.
Boston, V. E.
Boulos, P. B.
Bown, S. G.
Bozzetti, F.
Bradbury, A. W.
Bradley, J. A.
Bradley III, E. L.
Bramhall, S. R.
Brearley, S.
Brennan, M. F.
Brittenden, J.
Britton, B. J.
Brolin, R. E.
Brunt, L. M.
Büchler, M. W.
Buckels, J. A. C.
Budd, J. S.
Buess, G.
Bundred, N. J.
Burgess, P.
Burke, M.
Burnand, K. G.
Burney, R. E.
Butchart, E.

Callam, M. J.
Callaway, M.
Cameron, J. L.
Campbell, F. C.
Campbell, J. K.
Campbell, W. B.
Candinas, D.
Cant, P. J.
Carlson, G.
Carmichael, J.
Carnaille, B.
Carr, N. D.
Carr-Locke, D. L.
Carty, N.
Ceelen, W. P.
Chadwick, S. J. D.
Chalmers, R. T. A.
Chan, P.
Charnley, R. M.
Cheng, S. W. K.
Cheshire, N. J.
Cheslyn-Curtis, S.
Chetty, U.
Church, J. M.
Clark, O. H.
Coleridge Smith, P. D.
Collin, J.
Collins, R. E. C.
Cook, T. A.
Cooke, T. G.
Cooper, M. J.
Copeland, G.
Corall, R.
Corbally, M. T.
Corder, A. P.
Corlett, M. P.
Corson, J. D.
Cox, C. E.
Cross, F. W.
Crumplin, M. K. H.
Cruz, F.
Cuesta, M. A.
Cullen, P. T.
Cunliffe, W.
Curley, P. J.
Currie, I. C.
Cusick, E.

Dark, J.
Darke, S. G.
Darzi, A.
Davey-Smith, G.
Davidson, B. R.
Davidson, T.
Davies, A. H.
Davies, N.
de Beaux, A. C.
de Cossart, L. M.
De Cosse, J. J.
Deans, G. T.
Dehn, T. C. B.
Deitch, E. A.
Delbridge, L. W.
Delicata, R. J.
DeMeester, T. R.
Demetriades, D.
Dent, D. M.
Dervenis, C.
Desborough, J.
Diamond, T.
Dixon, A. R.
Dixon, J. M.
Donaldson, D. R.
Donohue, J. H.
Donovan, I. A.
Doran, J. D.
Dorudi, S.
Dralle, H.
Drew, P. J.
Drummond, G.
Duh, Q.-Y.
Dunlop, M. G.
Dunn, J.
Durdey, P.
Duthie, G. S.
Dwerryhouse, S.
Dykes, E.
Ebbs, S. R.
Eggermont, A. M. M.
Eikelboom, B. C.
Eklof, B. O.
Elder, J. B.
Elias, D.
Ellenbogen, S.
Ellis, I. O.
Emberton, M.
Eyre-Brook, I. A.

Faber, R. G.
Fagniez, P. L.
Falk, S. J.
Fan, S. T.
Farouk, M. O.
Farrands, P. A.
Fazio, V. W.
Fearon, K. C. H.
Fentiman, I. S.
Fielding, G. A.
Fielding, J. W. L.
Finch-Jones, M. D.
Fingerhut, A.
Fisher, J. E.
Fleshman, J. W.
Flye, M. W.
Fok, M.
Foley, R. J. E.
Forrester-Wood, C. P.
Forsythe, J.
Foster, M. E.
Fowkes, G.
Fox, A. D.
Francis, D. M. A.
Frankel, S.
Friend, P.
Friess, H.
Frilling, A.

Gaines, P. A.
Gajraj, H.
Galea, M.
Galland, R. B.
Gallegos, N. C.
Galloway, D.
Galloway, S. W.
Garden, O. J.
Gardiner, K. R.
Gee, A. S.
Geoghegan, J. G.
George, W. D.
Giddings, A. E. B.
Gilling-Smith, G.
Gillis, C. R.
Gingell, J. C.
Givel, J.-C.
Glass, R. E.
Glazer, G.
Go, P. M. N. Y. H.
Goh, H. S.
Goh, P. M. Y.

Gold, D.
Goldin, R.
Goodman, N. W.
Gooszen, H. G.
Gorey, T. F.
Goris, R. J. A.
Gotley, D. C.
Gough, M. J.
Gouma, D. J.
Grace, K.
Grace, P. A.
Grant, C.
Greenall, M.
Greve, J. W.
Griffin, S. M.
Grimley, R. P.
Gronroos, J. M.
Gullick, W. J.

Haagensen, D. E.
Haas-Kock, D. M. F.
Habib, N. A.
Haglund, U.
Hainsworth, P. J.
Hall, M. J.
Hall, N. R.
Hall, R. I.
Hallbook, O.
Halliday, A.
Halligan, S.
Hallissey, M.
Hamilton, G.
Hands, L. J.
Harder, F.
Harding, K. G.
Hardwick, R.
Harper, P. H.
Harris, P. L.
Harrison, B. J.
Hartley, J. E.
Hartley, M. N.
Harvey, R. F.
Hassan, M. A.
Hayes, N.
Hayes, P.
Heather, B. P.
Heidelmeyer, C.
Hemingway, D. M.
Henry, J.-F.
Herfarth, C.
Hershman, M. J.
Heyderman, R. S.
Heys, S. D.
Hishinuma, S.
Ho, Y.-H.
Hockerstedt, K.
Hodgson, H. J. F.
Hoekstra, H. J.
Hoile, R. W.
Holdcroft, A.
Holdsworth, J.
Holdsworth, P. J.
Holdsworth, R. J.
Holm, T.
Holmes, S. J. K.
Homer-Vanniasinkam, S.
Hopkinson, B. R.
Horgan, P. G.
Horrocks, M.
Hosie, K. B.
Housley, E.
Howell, S. J.
Hughes, S.
Huguet, C.
Hulten, L.
Hunt, T. K.
Hyland, J.

Ihse, I.
IJzermans, J. N. M.
Ilstrup, D. M.
Imrie, C. W.
Irvin, T. T.
Irvine, C. D.
Isozaki, H.
Izbicki, J. R.

Jaeck, D.
Jakeways, M. S. R.
Jamieson, C. W.
Jamieson, G. G.
Jamieson, N. V.
Jeekel, J.
Jensen, H. E.
Jensen, L. S.
Jeppsson, B.
Jewell, D.
Jiang, W. G.
John, T. G.
Johnson, C. D.
Jones, A.
Jones, A. S.
Jones, R. S.
Jones, S. M.

Kabala, J.
Kald, A.
Kalthoff, H.
Kamm, M. A.
Kapila, L.
Karakousis, C. P.
Karanjia, N. D.
Keane, F. B. V.
Keeling, D. M.
Keenan, R. A.
Kehlet, H.
Keighley, M. R. B.
Kelly, S. B.
Kennedy, R. H.
Kerin, M. J.
Kerr, D. J.
Khalil-Marzouk, J.
Khoo, D.
Kiff, E. S.
Kiil, J.
Kingsnorth, A. N.
Kirwan, W. O.
Kivilaakso, E.
Kmiot, W. A.
Kollias, J.
Koperna, T.
Koruth, N. M.
Kramps, J. L.
Kremer, B.
Krige, J. E. J.
Krukowski, Z. H.
Kumar, D.
Kutt, E.

Lai, E. C. S.
Lambert, D.
Lamerton, A. J.
Lamont, P.
Lane, I. F.
Lane, R. H. S.
Lau, J. W. Y.
Launois, B.
Layer, G. T.
Lazorthes, F.
Leaper, D. J.
Lee, P. W. R.
Lehnert, T.
Lehur, P. A.
Leinster, S. J.
Lennard, T. W. J.
Leung, H. Y.
Leveson, S. H.
Lewis, P.
Libutti, S. K.
Liem, M. S. L.
Lillemoe, K. D.
Lin, P.-W.
Linos, D. A.
Lloyd, A. J.
Lloyd, D. A.
Lloyd-Davies, E. R. V.
Lo, C. M.
Lo, C.-Y.
Lock, M. R.
Lodge, P.
London, N. J. M.
Longman, R.
Lonroth, H.
Lowe, G. D. O.
Lowry, S. F.
Lucarotti, M. E.
Ludlam, C. A.
Lundell, L.

Macdonagh, R. P.
MacFie, J.
Macintyre, I. M. C.
MacKinnon, A. E.
Maddern, G. J.
Madhavan, K. K.
Madiba, T. E.
Magee, T. R.
Mainprize, K. S.
Mandava, N. R.
Mansel, R. E.
Marescaux, J.
Markham, N. I.
Marsh, H.
Mason, G. R.
Mason, R. C.
Mather, S.
Mathias, D.
Mathieson, P. W.
Mayer, A. D.
McAnena, O. J.
McCloy, R. F.
McCollum, P. T.
McCulloch, P.
McDonald, P.
McFaul, R.
McGinn, F.
McGurk, M.
McHenry, C. R.
McKay, A. J.
McLeod, R. S.
McMahon, A. J.
McMaster, P.
McQueen, M.
McWhinnie, D. L.
Meagher, A. P.
Mealy, K.
Mee, A. S.
Meleagros, L.
Menzies, D.
Midwinter, M. J.
Mihai, R.
Mikhailidis, D. P.
Millar, A. J. W.
Miller, R.
Miyazaki, M.
Mjaland, O.
Mogensen, T.
Moghissi, K.
Monson, J. R. T.
Moorghen, M.
Moran, B. J.
Morgan, A.
Morgan, R. J.
Morgan, W. P.
Morran, C. G.
Morris, D. L.
Mortensen, N. J. McC.
Motson, R. W.
Mountford, R.
Mughal, M. M.
Mundy, A. R.
Munro, A.
Murphy, G.
Murray, F. E.
Murray, G. D.
Murray, W. R.
Muto, T.
Myhre, H. O.

Nagasue, N.
Nagorney, D. M.
Naylor, A. R.
Neal, D. E.
Nelson, H.
Neoptolemos, J. P.
Nesbakken, A.
Nevin, M.
Nicholls, R. J.
Nicholson, M. L.
Nicholson, S.
Niederle, B.
Nies, C.
Northover, J. M. A.
Norton, J. A.
Norton, S. A.
Nott, D. M.

Obertop, H.
O'Brien, P. E.
O'Dwyer, P. J.
Ogura, Y.
O'Higgins, N. J.
O'Sullivan, G. C.
Owen, W. J.

Påhlman, L.
Pain, J. A.
Palmer, K.
Parc, R.
Park, K. G. M.
Parker, D. R.
Parks, R. W.
Parrott, N. R.
Pasieka, J. L.
Paterson, D.
Paterson-Brown, S.
Peel, A. L. G.
Pemberton, J. H.
Penninckx, F.
Phillips, R. K. S.
Pisters, P. W. T.
Pitt, H. A.
Pleass, H.
Polk Jr, H. C.
Pollard, S. G.
Poston, G. J.
Powell, J. T.
Primrose, J. N.
Prinz, R. A.
Probert, C.
Proud, G.
Prys Roberts, C.
Pullan, R. D.
Pullyblank, A.
Puntis, M. C. A.
Purushotham, A. D.
Pye, G.
Pye, J. K.

Quick, C.
Qvist, N.

Radcliffe, A. G.
Raftery, A. T.
Raimes, S.
Rainey, J. B.
Rainsbury, R. M.
Ralphs, D. N. L.
Ramsay, G.
Rangecroft, L.
Rauwerda, J. A.
Rawlinson, J. N.
Raytor, Z.
Redmond, H. P.
Reece-Smith, H.
Rees, M.
Rennie, J. A.
Rew, D. A.
Reynolds, J. V.
Rhodes, M.
Rich, A. J.
Rivoire, M.
Robertson, C. S.
Robertson, G. S. M.
Rockall, T. A.
Roediger, W. E. W.
Rolles, K.
Rosin, R. D.
Ross III, A. J.
Rothmund, M.
Roukos, D. H.
Rowlands, B. J.
Royle, C. A. J. P.
Royle, G. T.
Royston, C. M. S.
Russell, C. F. J.
Rutgers, E. J. T.
Ryan, D.
Ryan, J. M.

Saadia, R.
Sackier, J. M.
Saclarides, T. J.
Saeger, H.
Sagar, P. M.
Sainsbury, J. R. C.
Sammon, A.
Sandelin, K.
Sanfey, H.
Sano, T.
Sarr, M. G.
Sasako, M.
Satsangi, J.
Schein, M.
Schirmer, B. D.
Scholefield, J. H.
Schouten, W. R.
Schwarz, M.
Schweizer, W.
Scott, D. J. A.
Scott, N. A.
Scott-Coombes, D.
Sear, J.
Selby, P.
Sellu, D.
Senapati, A.
Seow-Choen, F.
Shandall, A. A.
Shapiro, A. M. J.
Shearman, C. P.
Sheldon, G. F.
Shepherd, N.
Sheu, J.-C.
Shimada, M.
Shorthouse, A. J.
Shrenk, P.
Siewert, J. R.
Sim, A. J. W.
Simson, J. N. L.
Sitges-Serra, A.
Sjodahl, R. I.
Smedh, K.
Smith, F. C. T.
Smith, J. A. R.
Smith, J. H. F.
Smith, R.
Soeters, P. B.
Søreide, O.
Soutar, D.
South, L. M.
Speakman, C. T.
Spence, R. A. J.
Spencer, R. C.
Spicer, R. D.
Spitz, L.
Stamatakis, J. D.
Standen, G.
Stansby, G. P
Starling, J. R.
Stebbing, J. F.
Steele, R. J. C.
Steer, M. L.
Steger, A. C.
Stephenson, B. M.
Stevens, A.
Stiggelbout, A. M.
Stitz, R.
Stoker, J.
Stonebridge, P. A.
Stoppa, R.
Stotter, A. T.
Strachan, C. J. L.
Stringer, M. D.
Stuart, W.
Studley, J. G. N.
Sugarbaker, P. H.
Sugerman, H. J.
Sugimachi, K.
Sunderland, G. T.
Sutton, R.
Sweetland, H. M.

Talbot, R. W.
Tanaka, H.
Tanaka, K.
Tanaka, M.
Tate, J. J. T.
Taylor, E. W.
Taylor, I.
Taylor, P. R.
Tennant, W.
Terpstra, O. T.
Thomas, J. M.
Thomas, M. G.
Thomas, W. E. G.
Thompson, J. F.
Thompson, J. N.
Thompson, M. H.
Thompson, M. M.
Thompson-Fawcett, M. W.
Thomson, W. H. F.
Tibblin, S.
Tilanus, H. W.
Todoroki, T.
Toogood, G.
Tooke, J.
Toouli, J.
Traynor, O.
Treasure, T.
Troidl, H.
Trunkey, D.
Tveit, K. M.
Tytgat, G. N. J.

Ubhi, C. S.

Valori, R. M.
van Bockel, J. H.
van de Velde, C. J. H.
van der Werken, C.
van Eijck, C. H. J.
van Goor, H.
van Gulik, T. H. M.
Van Hee, R.
van Lanschot, J. J. B.
van Rij, A. M.
Vann Jones, J.
Varma, J.
Varty, K.
Veitch, P. S.
Vellacott, K. D.
Veronesi, U.
Verschueren, R. C. J.
Vickers, J.
Vipond, M. N.
Viste, A.
von Meyenfeldt, M. F.
von Smitten, K.

Walker, M. G.
Walls, J.
Walsh, T. N.
Ward, M. K.
Warren, B. F.
Warshaw, A. L.
Watanapa, P.
Waters, K. J.
Watkin, D. F. L.

Watkins, P.
Watson, A.
Watson, D. I.
Waxman, B.
Webb, A. J.
Webster, D. J. T.
Welbourn, C. R. B.
Wellwood, J. M.
Wexner, S. D.
Wheeler, M. H.
White, S. A.
Whiteley, M. S.
Widdison, A. L.
Wiggers, T.
Wildsmith, J. A. W.
Wilkins, D. C.
Willatts, S.
Williams, N. S.
Williamson, R. C. N.
Wilson, J. U.
Wilson, M. S.
Wilson, R. G.
Wilson, Y.
Windsor, J. A.
Winslet, M. C.
Winters, Z.
Wobbes, T. H.
Wolfe, J. H. N.
Wong, D. S. Y.
Wong, J.
Wood, R. F. M.
Woodhouse, C. R. J.
Woodward, A.
Wright, P. D.
Wyatt, M.

Yamaguchi, K.
Yeh, T. S.
Yeo, C. J.
Young, A. E.
Young, D. G.
Young, H. L.
Youngson, G. G.
Yu, W.